

# American Journal of Obstetrics and Gynecology

VOL. 58

OCTOBER, 1949

No. 4

## Original Communications

### HISTOCHEMICAL OBSERVATIONS ON GRANULOSA-CELL TUMORS THECOMAS, AND FIBROMAS OF THE OVARY

D. G. MCKAY, M.D., D. ROBINSON, M.D., AND A. T. HERTIG, M.D., BOSTON, MASS.

*(From the Mallory Institute of Pathology, Boston City Hospital, the Pathology Laboratory of the Free Hospital for Women, and the Departments of Pathology and Obstetrics, Harvard Medical School)*

RECENT histochemical techniques designed to indicate the cytologic localization of certain steroid hormones have been applied by Dempsey and Bassett<sup>1</sup> and McKay and Robinson<sup>2</sup> to the rat and human ovary, respectively. Steroid substances were found in the theca interna cells of the developing follicle, in the granulosa lutein and theca lutein cells of the corpus luteum and in the interstitial cells\* of the ovary. No reactive materials were found in the granulosa cells of the Graafian follicle or in the stroma cells of the ovarian cortex or medulla. Perhaps the most significant finding is the fact that in the Graafian follicle of both species steroidal substances are confined to the theca layer and are not present in the granulosa layer. This has been taken as evidence that the theca cell and not the granulosa cell is the one which produces the steroid hormone of the follicle. This idea is not a new one, since much experimental evidence in the past has indicated that it was true.

McKay and Robinson<sup>2</sup> also estimated the relative amounts of reactive materials present in the follicle and corpus luteum during the stages of development of these structures throughout the menstrual cycle. It was found that the amounts of steroid substances in the follicle and corpus luteum varied directly with the changing concentrations of urinary estrogen.

Because granulosa-cell tumors and thecomas are so frequently associated with an increased production of estrogenic hormone, and because fibromas are on occasion difficult to differentiate from thecomas, it was thought that the application to these tumors of the histochemical procedures outlined by Dempsey and Bassett<sup>1</sup> might reveal some information of theoretic and practical interest.

\*Interstitial cells are the large, isolated lipoid-laden cells which are occasionally seen lying in the cortical stroma.

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### Materials and Methods

A group of solid ovarian tumors including three granulosa-cell tumors, one thecoma with granulosa-cell nests, one luteinized thecoma, six thecomas, and two fibromas were available for study. For evidence of functional activity of these tumors the patient's history was examined for clinical evidence; when available the endometrium was examined and in one case of granulosa-cell tumor, estrogen studies were done on the patient's urine. Tissue fixed in formalin for twenty-four hours or longer was used. Serial sections were cut on the freezing microtome at 15 to 35 micron thicknesses. The 15 micron sections were stained with Sudan IV. For studies of fluorescence and birefringence, sections were mounted on slides in nonfluorescent glycerine. Observations on birefringence were made with a Spencer polarizing microscope, using plane-polarized light, while a fluorescent microscope using a beam of rays obtained by filtering the light of a carbon-arc lamp through a copper sulfate solution and a Corex filter No. 586 was used in determining fluorescence. Alternate sections were placed in acetone for twenty-four hours and then mounted in glycerine and subjected to these examinations.

Since the ovarian hormones are soluble in fat solvents, any substance which, after extraction with acetone, still reacts with the above reagents should probably not be regarded as a functioning ovarian steroid. Acetone extraction prevented all the above reactions in the normal human ovary and in this group of ovarian tumors.

Cholesterol, its derivatives, and their esters frequently form birefringent crystals, as do the ovarian steroids. This property, which is caused by the radial symmetry of the steroid molecules in liquid spherocrystals, is an expression of the molecular pattern of this class of compounds (Lison<sup>3</sup>). In the rat and human ovary two varieties of birefringence have been described. One is a fibrillar type, insoluble in acetone and associated with connective tissue bundles. The other is a crystalline birefringence, soluble in acetone and present in parenchymatous cells. The observations herein reported deal only with the latter variety of birefringence.

Bierry and Gouzon<sup>4</sup> demonstrated that purified estrogenic sterols exhibit a greenish-yellow fluorescence. In the rat and human ovary the cells of the theca interna emit a yellowish-green fluorescence as do the granulosa lutein cells, but the granulosa cells of the follicle exhibit a pale blue fluorescence.

The phenylhydrazine method of Bennett<sup>5</sup> was used. Alternate sections were extracted with acetone for twenty-four hours and then submitted to the phenylhydrazine reaction. Phenylhydrazine reacts with the carbonyl group of the reactive molecules to produce a yellow phenylhydrazone which can be visualized in the sections.

Sections were also treated with concentrated sulfuric acid. They were mounted on slides and the excess water was blotted off. A drop of concentrated sulfuric acid was placed on the tissue and a coverslip dropped on immediately. Sections extracted with acetone were similarly treated. Following the addition of sulfuric acid to reacting tissue, reddish-brown droplets or granules develop within sixty seconds. This is the Liebermann-Burchard reaction applied to tissues. It has been shown that steroids which possess unsaturated linkages will give this chromogenic reaction (Fieser<sup>6</sup>).

In addition, the Schiff or plasmal reaction of Feulgen and Voit<sup>7</sup> was used in several cases instead of the phenylhydrazine reaction. The Schiff reagent consists of basic fuchsin which has been decolorized by sulfurous acid. Aldehydes and some ketosteroids contain carbonyl groups active enough to cause this reagent to develop a violet color, according to Dempsey and Wislocki.<sup>8</sup>



Albert and LeBlond<sup>9</sup> and Gomori<sup>10</sup> have criticized the use of the phenylhydrazine reaction and the plasmal reaction as indicators of the presence of ketosteroids. These authors believe that the reactions in tissues to these reagents are due to the presence of acetals and that it is unlikely that positive plasmal reactions can be used to indicate steroids. Although Dempsey et al.<sup>11</sup> do not ascribe specificity to either the phenylhydrazine or the Schiff reaction, they do regard the Schiff reaction as one of a linked series which, taken together, provides evidence for the presence of these compounds.

In summary, any fat-soluble substance which has all these properties will have a polycyclic molecule with a double bond somewhere in the molecule and will have a carbonyl group attached to it. The ketosteroids have such a structure and give these reactions. Dempsey and Bassett<sup>1</sup> conclude that these reactions indicate the presence of certain ovarian hormones or their precursors and, more importantly, those tissues which fail to give the reactions are devoid of the steroid hormones.

## Results

### Granulosa-Cell Tumors

CASE 1.—Salem Hospital; S47-3. This 60-year-old white woman entered the hospital with a chief complaint of weakness, indigestion, and constipation. There was no history of postmenopausal bleeding. On physical examination a mass "the size of a grapefruit" was palpated in the left lower quadrant. The stool was guaiac negative and other laboratory tests were noncontributory. A laparotomy was performed. There was a large amount of bloody fluid in the abdomen. The omentum and small bowel were adherent to a friable ovarian mass which was removed manually. This was followed by severe hemorrhage. Following the operation the patient's condition became worse and she died two days postoperatively.

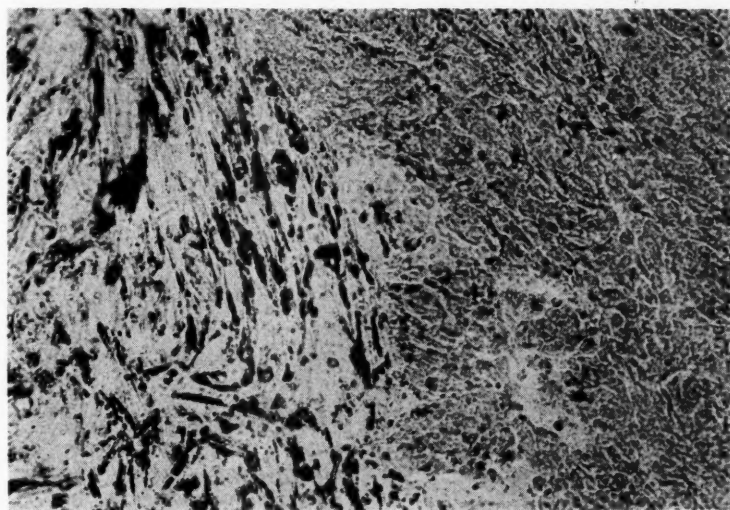


Fig. 1.—Photomicrograph of Sudan IV stain on granulosa-cell tumor of Case 1. The cellular mass on the right is made up of tumor cells with very few tiny, scattered sudanophilic droplets. The spindle-shaped, theca-like cells on the left contain large amounts of fat. These cells gave all the reactions of steroid hormones while granulosa cells were negative. ( $\times 400$ )

The pathologic specimen consisted of several pieces of firm, yellow-white tumor tissue associated with several small clots of blood. Microscopically, the tumor was made up of sheets and cords of small cells with round nuclei, indistinct cytoplasmic borders and occasional

Call-Exner bodies. Bands of connective tissue lay in between the tumor-cell masses. In several areas these connective tissue cells had assumed a plump, fusiform shape and had the appearance of theca interna cells.

Sudan IV stains revealed a few scattered, fine, red droplets in the granulosa cells and a large concentration in the theca-like cells of the connective tissue bundles (Fig. 1). There were no other reactive substances in the granulosa cells, but the plump connective tissue cells contained large quantities of birefringent crystals which gave a greenish-yellow fluorescence and reacted positively with phenylhydrazine and sulfuric acid.

**CASE 2.**—Faulkner Hospital; S48-1078. This 49-year-old white woman entered the hospital in June, 1948, with a chief complaint of vaginal bleeding for the past year. She had been spotting for this length of time with four episodes of heavy bleeding which occurred at irregular intervals and lasted for approximately three weeks. Physical examination revealed a soft, movable, midline mass rising to just above the symphysis. A total hysterectomy with removal of a right ovarian tumor was performed.

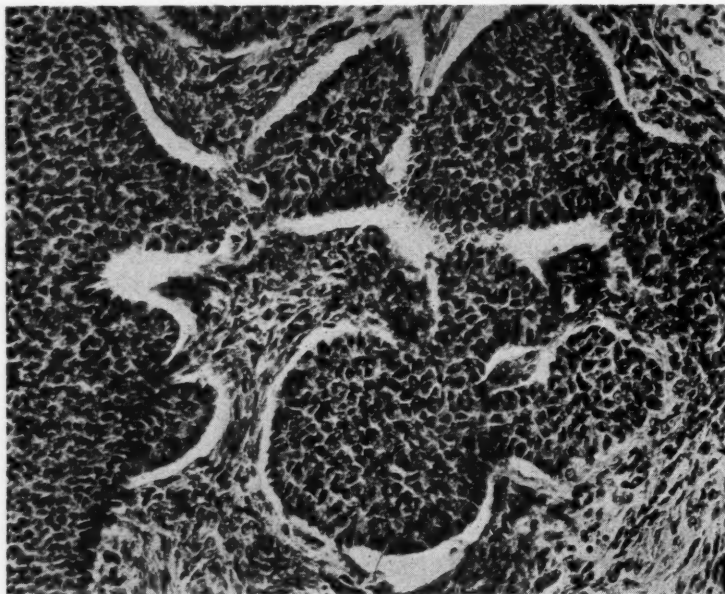


Fig. 2.—Photomicrograph of granulosa-cell tumor of Case 2. Phloxine-methylene blue stain. (×160)

The right ovarian mass weighed 275 Gm. and measured 11 cm. in diameter. It had a smooth, glistening surface and a central cavity. The cystic space in the center of the tumor was filled with fluid blood. The wall of the tumor measured from 0.5 to 3.0 cm. in thickness and consisted of solid, granular, pale yellow and pink tissue. The uterus measured 10 by 5.5 by 3.5 cm. and was not remarkable except for a very thick endometrium which measured up to 0.6 cm. in places. The tubes and the left ovary were not remarkable.

Microscopically the endometrium revealed a cystic hyperplasia.

Histologic sections of the tumor revealed cords and sheets of cells with round to oval nuclei arranged in palisades around the edges of the tumor-cell masses where they were in contact with the numerous bands of connective tissue. There were also numerous Call-Exner bodies in the sheets of tumor cells. The connective tissue cells were plump and fusiform and some intracytoplasmic vacuoles were observed in the section stained with phloxine-methylene blue (Fig. 2).

Histochemical studies revealed reactive materials in the large fusiform connective-tissue cells and none in the granulosa cells (Fig. 3).

CASE 3.—Boston City Hospital; S47-5794. This 74-year-old white woman entered the hospital with a chief complaint of abdominal pain of two days' duration. She had had anorexia and constipation for the past four months with a diminishing caliber of her stools. She had ceased menstruating twenty years prior to admission and had had no vaginal bleeding since that time. She had noticed no weight loss. On physical examination there was left lower quadrant tenderness. Pelvic examination revealed a low, hard, fixed cervix. There was no discharge or bleeding from the cervix. The uterus was enlarged posteriorly and the size of a four months' pregnancy. An extrinsic mass was palpated on rectal examination. A barium enema was done and revealed that the entire sigmoid was displaced laterally and upward by a mass arising from the pelvis and probably encircling the sigmoid colon. The radiologist's impression was that there was no intrinsic large bowel tumor. A sigmoidoscopy was done and was negative. Laboratory tests were not remarkable except that the stools were guaiac positive.

Five days after admission a cervical biopsy was taken and revealed a chronic cervicitis. No tissue could be obtained from the endometrial cavity on dilatation and curettage. Two days later a laparotomy was performed. There was no free fluid in the peritoneal cavity. The liver, gallbladder, stomach, spleen, kidneys and large bowel were normal. Some of the loops of small bowel were thin and dilated and contained fluid. There were numerous adhesions in the pelvis involving loops of small bowel, the dome of the bladder, the fundus of the uterus, and both adnexae. There was a large mass of necrotic tissue lying in the pelvis. A portion of the mass, the "size of a baseball," was removed manually and this was followed by brisk bleeding. Several metastases to the serosa of the small bowel were noted. Because of the bleeding no further surgery was done.

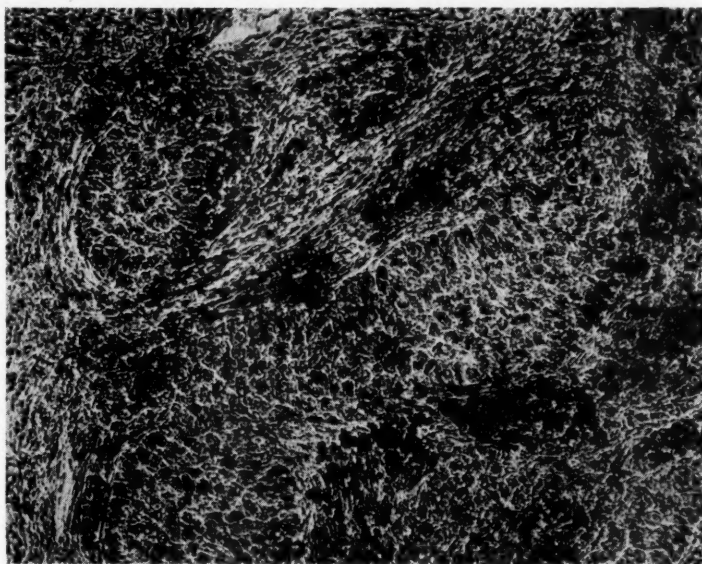


Fig. 3.—Photomicrograph of Sudan IV stain on granulosa-cell tumor of Case 2. Sudanophilic droplets absent in the cords of tumor cells but present in connective tissue cells and most abundant in those "theca-like" cells adjacent to the cords of tumor cells. ( $\times 160$ )

The urine contained no increase in estrogenic substances.

The patient did well postoperatively and was sent home for terminal care.

The pathologic specimen consisted of a soft, amorphous mass of tissue weighing 100 Gm. The tissue was gray to yellow with a few firm, white areas. There were scattered areas of necrosis and hemorrhage. Microscopically, the tumor consisted of sheets of cells with scant cytoplasm, poorly demarcated cell membranes, and round, irregular, vesicular nuclei

with a few scattered mitotic figures. In a few areas, the cells were arranged in tiny rosettes surrounding a central mass of acidophilic granular material, thus resembling Call-Exner bodies. There was a delicate, scant stroma in the regions immediately adjacent to the numerous blood vessels (Fig. 4).

When stained with Sudan IV, a few tiny, intracytoplasmic red droplets were seen in the granulosa cells. No birefringent crystals were present in the tumor tissue and the latter tissue gave a negative reaction to sulfuric acid and Schiff's reagent. The granulosa cells gave a pale blue fluorescence. There were no sudanophilic droplets in the stromal cells, nor did they give any reactions consistent with the presence of steroid substances.

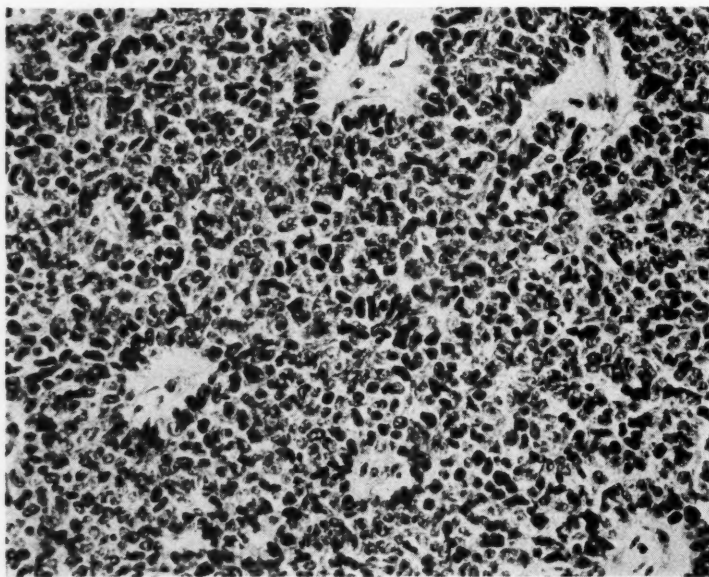


Fig. 4.—Photomicrograph of granulosa-cell tumor of Case 3. Phloxine-methylene blue stain. ( $\times 400$ )

### Active Thecomas

#### Thecoma With Granulosa-Cell Nests

CASE 4.—Boston City Hospital; S47-3852. This 65-year-old white woman entered the hospital with a chief complaint of a mass in the abdomen which had been noticed for the past two years. She gave no history of postmenopausal bleeding. A large abdominal mass, thought to be a uterine leiomyoma, was palpated and a laparotomy performed with removal of the ovarian mass as well as the uterus, tubes, and the other ovary.

The pathologic specimen consisted of a mass measuring 22 by 17 by 16 cm. which weighed 3,800 Gm. It had a smooth, rounded, glistening surface. The cut surface revealed large, yellow nodules, 5 to 6 cm. in diameter, with thick, interlacing bundles of dense, white, fibrous tissue. The uterus was small but the endometrium was velvety and thick and piled up into numerous sessile, polypoid masses. Microscopically the tumor was made up of interlacing, whorled bundles of plump, spindle-shaped cells interspersed with bands of dense, collagenous connective tissue. Scattered throughout the tumor were small nests of granulosa cells, many of which contained Call-Exner bodies (Fig. 5).

There was cystic hyperplasia of the endometrium.

The dense collagenous connective tissue bands did not take up the Sudan IV, whereas the plump, spindle-shaped cells showed numerous intra- and extracellular red droplets. The granulosa-cell nests also revealed a few scattered, extracellular fat droplets. These were fewer in number than those in the theca cells. Steroid substances, i.e., birefringent crystals



exhibiting a faint, yellow-green fluorescence and reacting with sulfuric acid and Schiff's reagent were present in the plump theca cells but were absent in the collagenous connective tissue and were scant in the granulosa cell nests.

#### Thecoma With Foci of Luteinization

CASE 5.—Faulkner Hospital; S46-1514. This 32-year-old white woman entered the hospital with a chief complaint of a lump in the right lower quadrant. For the past five years she had had marked menstrual irregularities, consisting of periods of amenorrhea lasting as long as three months and followed by a scanty blood flow lasting one to two days. The two periods preceding entry had been characterized by an excessive flow for one day. On physical examination a plum-sized mass was palpable in the right lower quadrant. A dilatation and curettage and bilateral salpingo-oophorectomy were done.

The gross specimen consisted of two firm, irregular, gray and gray-pink masses. The larger was in the shape of three connected spheres which measured 16 by 8 by 5 cm. when stretched out. The smaller mass was ovoid and measured 7 by 5 by 3 cm. The tumors were covered with a dense, tough, glistening tissue. On section they revealed a dense, gray, whorled tissue with a few foci of soft, yellow tissue scattered throughout. Microscopically, the tumor consisted of whorls and bundles of plump, spindle-shaped cells. In several areas the cells were extremely large with a vacuolated to clear cytoplasm and with the nuclei located at one side of the cell.

The endometrium revealed a secretory response.

Sudanophilic droplets and reactive substances were present in the spindle-shaped theca cells but were seen in greatest amount in the luteinized theca cells. It is noteworthy that in this tumor there appeared to be a much larger amount of sudanophilic material than material giving the steroid reactions.

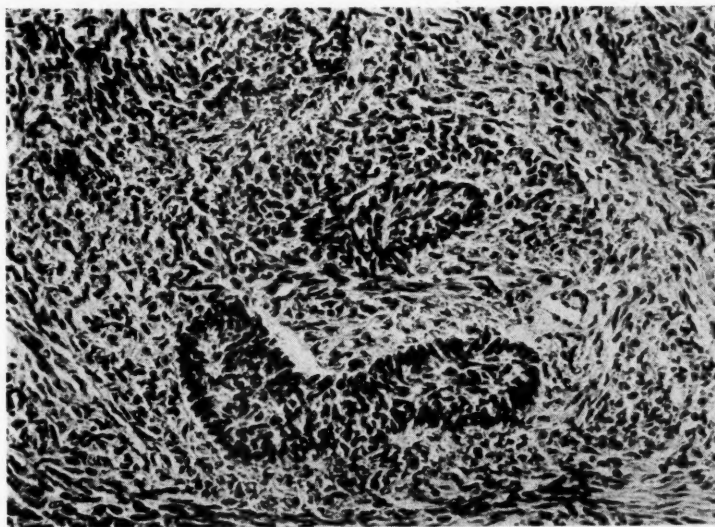


Fig. 5.—Photomicrograph of thecoma with granulosa-cell nests (Case 4). Phloxine-methylene blue stain. ( $\times 400$ )

CASE 6.—Massachusetts Tumor Diagnostic Service; S47-4911. This 36-year-old white woman entered with a chief complaint of pain in the epigastric region and dysmenorrhea for the past five to six months. She had not had dysmenorrhea prior to this time. In addition, she complained of an excessive flow at each of the previous five menstrual periods. The bleeding had lasted for seven to eight days, whereas it had never before lasted for longer than three days. Physical examination revealed a retroverted uterus and tenderness in both lower quadrants. A panhysterectomy was performed.

The pathologic specimen consisted of the uterus, both tubes, and ovaries. In the left ovary was a corpus luteum. In the right ovary there was a mass measuring 7 by 4 by 3.5 cm., which had a smooth, glistening, rounded surface and which on section revealed a whorled, yellow, solid mass of fibrous tissue. Microscopically it was a typical thecoma.

The endometrium was in the secretory phase of the cycle.

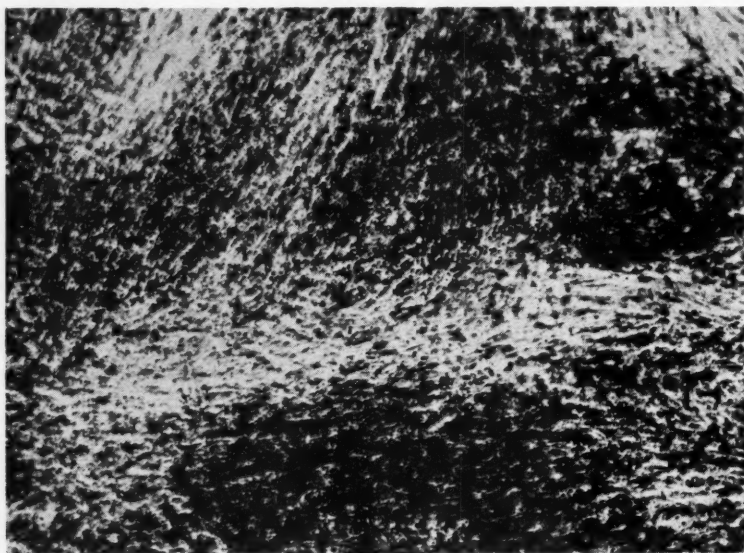


Fig. 6.—Photomicrograph of Sudan IV stain on thecoma of Case 6. Fat droplets are present intra- and extracellularly in bundles of plump, spindle-shaped theca cells but are absent in collagenous connective tissue bands and hyaline plaques. ( $\times 400$ )

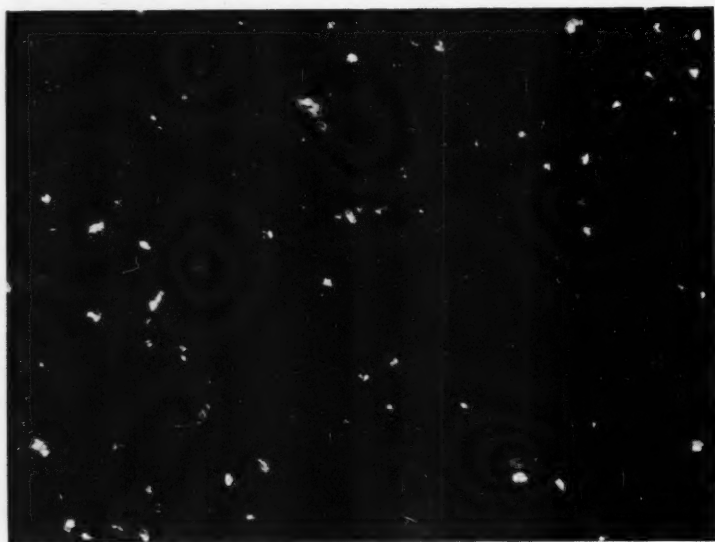


Fig. 7.—Photomicrograph of frozen section of thecoma taken between crossed Nicol prisms. Birefringent crystals are present in theca cells. Birefringence of the fibrillar variety can be seen in the collagenous connective tissue bands. ( $\times 400$ )

Histochemical studies revealed a large number of sudanophilic droplets in the bands of spindle-shaped cells (Fig. 6), but none in the collagenous tissue or in the hyaline plaques. There were numerous birefringent crystals present (Fig. 7) and the tissue gave a positive reaction to sulfuric acid and the Schiff reagent.

CASE 7.—Free Hospital for Women; S48-1483. This 65-year-old white married woman entered the hospital in January, 1948, with a chief complaint of vaginal bleeding. She had noted staining for the past six months and a heavy flow of bright red blood one week prior to entry. The last menstrual period had occurred fifteen years previously. A dilatation and curettage were performed which yielded distinctly hyperplastic endometrium. An incidental cervical polypectomy was also done. Following these procedures there was no further bleeding.

Because of the hyperplasia of the endometrium, which suggested the possibility of an ovarian tumor, she was brought back to the hospital in April, 1948, at which time a complete hysterectomy was done. The pathologic specimen consisted of the uterus, both tubes, and ovaries. The right ovary measured 1.5 by 2.5 by 3.5 cm. and was completely replaced by a nodular, yellow tumor with a whorled, gray-yellow cut surface and a 0.2 cm. cyst in its center. The left ovary was atrophic. Microscopically the tumor was a typical thecoma. Histochemical studies revealed a large quantity of reactive substances in the theca cells. The endometrium was hyperplastic with numerous large cystic glands.

CASE 8.—Free Hospital for Women; S47-4382. This 57-year-old white woman entered the hospital in 1947 with a prolapse of the uterus, an enterocele, and a cystocele. Her first admission had been in 1935, eight years after the delivery of her last child, when she entered with a chief complaint of menorrhagia with alternating periods of amenorrhea and periods of bleeding lasting up to six weeks. At that time a dilatation and curettage were done as well as a plastic repair of the prolapse, and a "sterilization dose" of radium was placed in the endometrial cavity. The endometrium at that time was atypical in appearance and was diagnosed endometrial dysplasia. Her menses ceased in 1935 but she had noted spotting in the several months prior to her admission in October, 1947. Physical examination revealed a mass in the pelvis as well as an enterocele, a cystocele, and a prolapse. The uterus, tubes, left ovary, and right ovarian tumor were removed and a plastic repair of the perineum was done.

The right ovarian mass weighed 620 Gm. and measured 14 by 10 by 8 cm. It had a smooth, rounded, white, glistening surface and on section revealed a solid, white, fibrous cut surface with streaks of yellow. Microscopically it was a typical thecoma with whorled bundles of spindle-shaped cells, among which were scattered the characteristic pink hyaline masses. The endometrium was of the senescent variety.

A few sudanophilic droplets and reactive steroid substances were present in small concentrations. The steroid material was confined to the plump, spindle-shaped cells and was absent in the collagenous connective tissue bundles and the hyaline masses.

#### Inactive Thecomas

CASE 9.—Free Hospital for Women; S48-1560. This 44-year-old white woman entered the hospital in August, 1947, with a chief complaint of intermenstrual bleeding and a more profuse flow with her periods. This abnormal bleeding was of three to four months' duration. Previously her menstrual cycle had been normal. Physical examination revealed a large, lacerated cervix attached to which was a small polyp. The latter was excised and a dilatation and curettage performed. Histologic examination revealed a benign cervical polyp and secretory endometrium.

The patient was discharged from the hospital and re-entered in April, 1948, complaining of two episodes of intermenstrual bleeding. A complete hysterectomy and left salpingo-oophorectomy were done. The uterus was not remarkable and the endometrium was of the secretory type with no evidence of hyperplasia. A solid tumor measuring 1.5 by 1.5 by 2.5 cm. was present in the left ovary at one pole. At the other pole was a hemorrhagic corpus luteum. The tumor was firm and on section revealed a white cut surface. Histologically, this tumor contained hyaline plaques and bands of dense collagenous tissue and was a typical thecoma of the inactive variety. There were no reactive substances anywhere in this tumor.

CASE 10.—Free Hospital for Women; S48-1775. This 75-year-old white woman entered the hospital with a chief complaint of "pain in the pelvis." There was no history of postmenopausal bleeding. Physical examination revealed a 4 by 3 inch mass in the left lower quadrant. A total hysterectomy and bilateral salpingo-oophorectomy were performed. The left ovary was replaced by a firm, solid tumor mass measuring 7 by 5.5 by 4.5 cm. The external surface was smooth, white, and glistening. On section it appeared white with small, scattered, yellow patches. The uterus contained several small leiomyomas.

Histologically, the ovarian tumor was made up of dense whorls of collagenous connective tissue with the characteristic pattern of an inactive thecoma. The endometrium was of the senile variety with a few scattered cystic glands, interpreted as the residuum of a previous hyperplasia. Histochemical examination revealed no steroid substances in this tumor.

CASE 11.—Free Hospital for Women; S47-5099. This 63-year-old white woman entered the hospital with a chief complaint of intermittent bleeding during the previous year and left lower quadrant pain for the previous three months. Endometrial curettings revealed adenocarcinoma of the uterine body. A hysterectomy and oophorectomy were done. In the left ovary was a firm, irregular mass measuring 5 by 4 by 3.5 cm. with a smooth, glistening surface. On section the cut surface was hard and had a whorled, white, fibrous appearance. Microscopically this tumor was made up of whorls of connective tissue with hyaline masses scattered throughout. Histologically it was a typical though inactive thecoma.

There were no sudanophilic droplets in this tumor and none of the tests for steroid substances was positive.

#### Fibromas

CASE 12.—Free Hospital for Women; S46-3716. This 19-year-old white woman entered the hospital with a chief complaint of left lower quadrant pain which had become worse in the last year. The pain was more severe at the onset of menstruation. She also complained of urgency and pressure on the bladder. The patient had also noticed that her breasts were sore at the time of menstruation. There was no history of amenorrhea, menorrhagia, or metrorrhagia. On physical examination a firm, suprapubic mass was palpated which displaced the uterus posteriorly. A laparotomy was performed and the mass removed from the left ovary. The patient continued to have regular menses and the breasts continued to be sore.

The pathologic specimen consisted of a tumor mass weighing 220 Gm. and measuring 7 by 8 by 7 cm., with a smooth, glistening, gray-white surface. On section the cut surface was firm, white, and presented a whorled, fibrous appearance. Microscopically, this tumor was made up of dense bands of collagenous connective-tissue cells. Neither plump, spindle-shaped cells nor hyaline masses were present. Curettage was done and revealed a menstrual endometrium.

There were no sudanophilic droplets or reactive steroid substances in this tumor.

CASE 13.—Salem Hospital; S47-455. This 65-year-old white woman entered the hospital with a chief complaint of pain in the right groin. She had had a normal menopause and there was no history of postmenopausal bleeding. A small tumor was palpated in the right ovary which was removed at a subsequent laparotomy.

The ovary contained a small, firm mass measuring 3 by 2 by 2 cm., with a rounded, smooth, glistening surface. On section it presented a firm, white, whorled, fibrous cut surface. Microscopically, it was composed of dense, collagenous connective tissue bundles and was characteristic of an ovarian fibroma.

There were no sudanophilic droplets or reactive steroid substance in this tumor.

#### Ovarian Carcinoma

CASE 14.—This 57-year-old white woman entered the hospital for the first time in March, 1940. Her chief complaint was menorrhagia. She had been bleeding continuously for the past five months. Her last regular period had been in October, 1939. Prior to that time



there had been no menstrual irregularities. A hysterectomy and left oophorectomy were done during this admission. The right ovary appeared normal at the time of operation. The left ovary contained numerous follicle cysts and the uterus was not remarkable except for a slight endometrial hyperplasia. She was discharged and remained well until April, 1945, when she re-entered with a complaint of right lower quadrant pain lasting for two months, which had suddenly become severe on the day of admission. A cyst was palpated in the right lower quadrant. A laparotomy was performed and a large mass of clotted blood and soft, yellow tumor tissue was found in the region of the right ovary. This mass was resected and measured 14 by 6 by 4 cm. Microscopically it consisted of sheets of cells with round to spindle-shaped nuclei with one or more prominent nucleoli. The cell membranes were indistinct and there was a very small amount of cytoplasm. There were numerous round, clear areas in between the tumor cells. In some areas the tissue had a reticulated appearance because of the great numbers of these clear spaces. Broad bands of fibrous tissue surrounded the sheets of tumor cells.

After the removal of the tumor the patient remained well until several months before her last entry in April, 1948, when she developed "discomfort in the lower abdomen." A mass was noted and it seemed to the patient to have increased in size. Physical examination revealed a palpable, cystic mass in the right side. At operation it was found to be adherent to the sigmoid colon and the bladder, and was removed with difficulty.

The pathologic specimen consisted of a soft, glistening, yellow mass of tissue measuring 8 by 10 by 6 cm. It had the appearance of fat and was lobulated. Microscopically, the tumor was identical with the portion of tumor removed in 1945.

A twenty-four-hour urine sample was collected and revealed no increased follicle-stimulating hormone or estrogen excretion.

Tests for steroid substances revealed large collections of reactive materials in the clear spaces in between tumor cells. In large areas of the tumor the cells were devoid of steroid substances, but in others were found in the cytoplasm of the tumor cells. There was also a small amount of reactive material in some of the connective-tissue cells of the interlacing fibrous bands.

In addition to these tumors, a Brenner tumor was available for study. The tumor gave no evidence of hormone production, which was to be expected, nor did it contain steroid substances on the histochemical examinations used in these investigations.

### Discussion

Because this is a small series of tumors, it would seem unwise to attempt to draw any final conclusions from it. In the following discussion those tentative conclusions which are suggested by the results are presented.

Although the granulosa cells of ovarian tumors, as well as those of normal ovaries, contain a few tiny intracytoplasmic sudanophilic droplets, they give none of the histochemical reactions which indicate the presence of ketosteroids. The tumor of Case 1 showed a "theca-cell" response of some of the connective tissue cells of the stroma, and these cells contained reactive substances. Unfortunately, no precise information was available which would indicate whether or not it was an estrogenically active tumor. The tumor of Case 2 was associated with a demonstrable increased estrogen production and followed this pattern.

This finding is in essential agreement with previous studies of a similar nature on estrogenic ovarian tumors. Schiller<sup>12</sup> found lipid mainly in the connective tissue bundles in between the granulosa cells. Greenblatt et al.<sup>13</sup> describe three granulosa-cell tumors, the first of which when stained with

Sudan IV showed that the granulosa cells contained minute sudanophilic droplets in small numbers, but large amounts of this lipoid material were present in the surrounding "theca-like" spindle-shaped connective-tissue cells. This suggested to them that the granulosa cells had exerted an influence on the connective tissue immediately in contact with them in much the same way as granulosa cells of the developing Graafian follicle induce the immediately surrounding ovarian stroma to produce theca cells. The tumor cells of their second granulosa-cell tumor had intra- and extracellular sudanophilic droplets which were not birefringent, indicating, therefore, that there was no appreciable steroid material present. Their third tumor was a "theca-granulosa-cell tumor" similar to the fourth tumor in our group. Both of these tumors had plugs of granulosa cells containing small amounts of sudanophilic material. The adjacent stroma, furthermore, had a marked accumulation of fat which was birefringent in Greenblatt's case and gave all the reactions for steroid substances in our case. Greenblatt noted that the fat in the granulosa cells was not anisotropic.

These findings suggest that it is the "theca-cell" component of the granulosa-cell tumor which secretes the estrogenic hormone and not the granulosa cells. This is, therefore, similar to the situation that exists in the Graafian follicle.

Experimentally, the evidence is manifold that the granulosa cell does not produce estrogen and that theca cells do. Zondek and Aschheim<sup>14</sup> demonstrated that implantation of granulosa cells does not produce estrus in the castrate animal. Bell<sup>15</sup> castrated animals and grafted ovarian cortex from which follicles had been removed, leaving only theca cells. These animals developed a normal estrous cycle. The x-ray studies of Hüssy and Wallart<sup>16</sup> are more convincing. They irradiated the ovaries and produced follicular degeneration with a resultant proliferation of theca cells. The ovaries were converted into masses of theca cells that had definite hormonal activity. Melnick and Kanter<sup>17</sup> stated that the hormone in granulosa-cell tumors is perhaps derived from the adjacent mesenchyme and not from the tumor cells themselves. The histochemical studies herein reported tend to support this thesis.

Theca-like cells are probably present in most granulosa-cell tumors. Traut et al.<sup>18</sup> have demonstrated that the theca interna of the Graafian follicle contains a fine reticulum network which is absent in the granulosa layer. They applied the reticulum stain to granulosa-cell tumors and became convinced that in the well-differentiated or folliculomatous types of granulosa-cell tumor, as well as in the more undifferentiated types, representatives of both cellular layers of the Graafian follicle were present. In other words, many so-called granulosa-cell tumors contain considerable quantities of thecal elements.

There is but brief mention in the literature of non-functioning granulosa-cell tumors. Ewing<sup>19</sup> states that small, silent granulosa-cell tumors have been accidentally discovered at autopsy.

Hodgson et al.<sup>20</sup> in a study of sixty-two granulosa-cell tumors found four small tumors associated with atrophic endometrium—presumptive evidence that they were nonestrogenic. It is believed that our Case 3 is an example of a nonfunctioning granulosa-cell tumor. Like the other granulosa-cell tumors, its cells are devoid of reactive materials but unlike most of these tumors it contains no hormonally active thecal component. Urinary estrogens in this patient were not elevated and there was no history of postmenopausal bleeding.

The diagnosis in Case 3 can scarcely be in doubt. The tumor had several of the gross features of granulosa-cell tumor; other common sources of intra-

abdominal carcinoma such as cervix, corpus uteri, bowel, etc., were made extremely unlikely by the various examinations mentioned previously; and finally, the tumor had the histologic characteristics of granulosa-cell tumor including Call-Exner bodies. The fact that it had metastasized locally to the peritoneum is not against the diagnosis, since Novak<sup>21</sup> reports that 28 per cent of granulosa cell tumors in his series were malignant.

Indeed, it would be quite strange if an occasional nonestrogenic granulosa-cell tumor did not present itself. There are few, if any, endocrine tissues elsewhere in the body which do not give rise to nonfunctioning tumors on occasion.

The presence of sudanophilic droplets which give the histochemical reactions of the steroid hormones in thecomas is in accordance with the findings of Melnick and Kanter<sup>17</sup> in two cases of thecoma. These authors found large quantities of sudanophilic material which was birefringent. Greenblatt et al.<sup>13</sup> reported that in thecomas the lipoids were abundant, where the connective tissue cells took on a plump, fusiform, epithelioid character, and that these lipoids were birefringent. In the present series of tumors the reactive materials were present in much larger amounts in the active thecomas than in either of the granulosa-cell tumors. It is interesting to note in this connection that Geist<sup>22</sup> states that the hormone content of the theca tumor in the one case examined was far greater in amount than that reported for granulosa-cell tumors.

In this study the thecomas divided themselves into two types—those that contained and those that did not contain reactive steroid substances. With one exception, Case 8, those thecomas which contained histochemically demonstrable steroids gave definite evidence of functional activity. Even in that case there was a history of irregular bleeding following an artificial menopause which might be evidence that the tumor was active in spite of the presence of a senescent endometrium. Parenthetically, it is interesting to speculate on the possible role the radiation may have played in producing this thecoma. Thecomas are easily produced in experimental animals by irradiation, and Traut and Butterworth<sup>23</sup> have mentioned a human case in which radiation may have resulted in the production of an estrogenic ovarian tumor.

At the Free Hospital for Women such a tumor followed the accidental exposure to x-rays in the case of a young woman who accompanied her mother while the latter was treated for carcinoma of the breast.

Conversely, the thecoma which was devoid of histochemically demonstrable steroids was likewise associated with no demonstrable increased estrogen secretion. This division of thecomas into two groups, an active and an inactive type, has been suggested by Traut and Butterworth.<sup>23</sup> It seems likely that a theca cell in a theca-cell tumor may go through a stage of active secretion, followed by an inactive phase, very much like the theca cell of the Graafian follicle which undergoes atresia. In Case 9 the history of menstrual irregularities several months prior to the time of removal of the tumor suggests that this thecoma had at one time been active but was inactive at the time of removal. It would seem that histochemical studies offer a good means for differentiating an active from an inactive thecoma.

The two cases of fibroma that were studied were free of steroid substances as was to be expected. The histochemical techniques, therefore, enable one to differentiate an active thecoma from a fibroma, but of course will not differentiate an inactive thecoma from a fibroma. The differentiation of the latter two tumors rests upon the morphologic appearance, but even this is often difficult.



The last tumor, Case 14, is not considered by the authors to belong in this series but is included because it was diagnosed a granulosa-cell tumor by several other pathologists. In our opinion it cannot be considered a granulosa-cell tumor from either the functional or the morphologic standpoint. The tumor, to the best of our knowledge, was nonestrogenic. There was no increased estrogen in the patient's urine and no elevation of follicle-stimulating hormone. No clinical evaluation of hormone production could be made since the uterus had been removed several years prior to the discovery of the tumor. Histologically, the tumor was made up of solid masses of elongated cells with prominent nucleoli and interlacing bands of connective tissue. There were no Call-Exner bodies and the cells were spindle-shaped rather than plump, rounded cells as one usually sees in most granulosa-cell tumors. The histochemical studies revealed reactive substances in the tumor cells and in the connective tissue cells as well. These probably represent deposits of cholesterol and cholesterol esters. Although the exact diagnosis of this tumor is in doubt, the authors consider it to be a solid ovarian carcinoma of undetermined type.

### Summary

Histochemical studies, designed to demonstrate the location of ketosteroids, were carried out on three granulosa-cell tumors, eight thecomas and two fibromas of the ovary. The functional state of each tumor was evaluated on the basis of the patient's history or the state of the endometrium, and in one case the estrogen concentration in the urine.

In general, the reactive materials were present in the theca cells of thecomas and in the theca-like cells of the granulosa-cell tumors. From these and other considerations it seems likely that the thecal component of granulosa-cell tumors, rather than the tumor cells themselves, is concerned in hormone production. One case of a nonestrogenic or "pure" granulosa-cell tumor is reported.

Steroid substances were not present in the collagenous connective tissue of thecomas nor in the two fibromas. It is concluded that histochemical studies are capable of differentiating active thecomas from inactive thecomas and fibromas.

We wish to express our appreciation to Dr. D. A. Nickerson of Salem Hospital, Dr. P. LeCompte of the Faulkner Hospital, and Drs. Olive Gates and S. Warren of the Tumor Diagnostic Service of the Massachusetts Department of Public Health for generously furnishing some of the specimens used in this study.

### Addendum

Since submitting this paper for publication, we have had a note by Boscott and co-workers<sup>24</sup> called to our attention. These authors tested three pure samples of desoxycorticosterone with Feulgen's plasmal reaction after treatment with cold mercuric chloride and found no evidence of oxidation of desoxycorticosterone to aldehyde by mercuric chloride. They conclude that this technique cannot be relied upon to demonstrate the cytological location of alpha hydroxyketones.

It should be noted, however, that the reactivity of the carbonyl linkage in different ketosteroids varies a great deal, and some do give this reaction (E. W. Dempsey, personal communication).

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## CARCINOMA OF THE OVARY\*

MALCOLM S. ALLAN, M.D., AND ARTHUR T. HERTIG, M.D., BROOKLINE, MASS.

*(From the Pathology Laboratory, Free Hospital for Women, Brookline, and  
The Department of Pathology, Harvard Medical School)*

THIS is a complete analysis of all cases of primary ovarian carcinoma treated at The Free Hospital for Women during a period of forty-three years, from 1903 through 1945. An attempt has been made to glean all possible information from this large group of cases which, through the years, has been carefully studied from clinical and pathological standpoints.

According to the hospital record room indices, 1,740 proliferative ovarian tumors† have been classified during this period of study. Of this number, 265 (15.2 per cent) have been considered malignant. Pemberton<sup>1</sup> analyzed 149 of these in 1938 and reported his results in 1940. A considerably different approach has been used in the present study, however, and 116 additional tumors, including other categories such as granulosa cell carcinoma, have been reviewed.

All cases were treated by surgery and many by x-ray as well. Operations were performed on both ward and private patients by various members of the staff. Therefore, this is actually a staff report.

### Method

The hospital records were searched for definite and borderline cases of primary ovarian carcinomas. Records of these cases were then carefully abstracted. All pathological reports were reviewed and the microscopic sections on every case re-examined, repeatedly in many cases. All borderline cases, as well as those that proved difficult of diagnosis, were re-evaluated by one of us (ATH). In the past, many of these difficult sections had been examined by Drs. Robert Meyer, Tracy Mallory, Shields Warren, S. Burt Wolbach, George Van S. Smith, Frank A. Pemberton, and others.

Admittedly, it has been difficult to determine microscopically whether some of these tumors were malignant or not. Some of our diagnoses would undoubtedly provoke agreement among some pathological authorities and disagreement among others. In some of the borderline cases, we have seen the host of such a tumor proceed through metastasis and on to death in a few months. Such cases frequently were used for comparative purposes in some of our decisions. Again, several tumors, notably those of the gross solid type, which defied every attempt at microscopic classification, were relegated to an undifferentiated group. Other authors would probably prefer to term these solid adenocarcinomas but we found a few partially cystic tumors which were just as undiagnosable as the solid types and elected to establish an undifferentiated group.

A classification was chosen which seemed to have practical significance from both clinical and pathological viewpoints. The primary classification was made on the basis of microscopic pathology. Further differentiation was made according to gross characteristics so as to be of value to the surgeon.

\*Read in part at the April, 1948, meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons at Boston, Mass.

†Cases of carcinoma were taken from the pathology files and the figures concerning the incidence of all ovarian tumors were taken from the record room files.

Grading of the tumors, although often said to be unreliable, has been attempted according to established methods. Pemberton before us, Taylor and Greeley<sup>2</sup> and others have found such methods reliable. Our policy has been to consider the well-differentiated tumors as Grade I. The wildly anaplastic tumors with a profusion of mitoses and bizarre cells were denoted as Grade III. All the others gravitated to the Grade II group.

Short of FBI proceedings, the cases have been exhaustively followed through the years. Since 1942, 26 cases have received treatment. These cases have not had a five-year follow-up and this number has been deleted from any computation involving salvage figures.

The information thus gathered from many sources was then classified and recorded on punch-cards of our own design so that an infinite number of relationships could be established. Some of these relationships are shown on the tables to follow. For the sake of clarity and brevity, relationships of the minor subdivisions have been included only when considered especially significant or interesting.

### Incidence

Over a period of 45 years a total of 1,740 proliferative ovarian tumors have been encountered. In Table I the incidence of various benign types are compared to each other and to their malignant counterparts when possible.

TABLE I. INCIDENCE OF OVARIAN TUMORS

MICROSCOPIC TYPE	BENIGN TUMORS		MALIGNANT TUMORS		BENIGN AND MALIGNANT TUMORS	
	NUMBER	PER CENT OF TYPE	NUMBER	PER CENT OF TYPE	NUMBER	PER CENT OF ALL TYPES
Serous	347	68.4	160	31.6	507	29.1
Pseudomucinous	361	87.0	54	13.0	415	23.8
Unclassified cystadenoma	36	100.0			36	2.1
Dermoid cyst	313	99.0	3	1.0	316	18.2
Granulosa cell	26	70.3	11	29.7	37	2.1
Fibromas	359	100.0			359	20.6
Brenner	20	100.0			20	1.1
Miscellaneous benign*	13	100.0			13	.7
Undifferentiated carcinoma			24	100.0	24	1.4
Hypernephroma (Grawitz)			6	100.0	6	0.3
Endometriocarcinoma			3	100.0	3	0.2
Dysgerminoma			2	100.0	2	0.1
Carcinosarcoma			2	100.0	2	0.1
	1,475	84.8	265	15.2	1,740	100.0

\*Including leiomyoma, arrhenoblastoma, adenomyoma, and paraganglioma.

Dockerty<sup>3</sup> states that 15 per cent of all ovarian neoplasms are of the benign serous type and that the ratio of benign serous to benign pseudomucinous types is 3 to 4. Our incidence for benign serous type is 20 per cent and the ratio of serous to pseudomucinous is nearly 1 to 1. Novak<sup>4</sup> indicates this ratio to be about 1 to 1. Dockerty<sup>3</sup> also states that the number of benign pseudomucinous tumors constitutes from 20 to 30 per cent of all ovarian neoplasms. Our figure for this type approximates 21 per cent. In this series, dermoid cysts have occurred slightly less often than benign serous tumors.

When considering the incidence of malignant ovarian tumors, we found 265 of 1,740 neoplasms to be malignant. This is a frequency of 15.2 per cent which compares with Meyer's<sup>5</sup> findings of 14.9 per cent, Goldsmith's<sup>6</sup> 24 per cent, and Barzilai's<sup>7</sup> estimates of 21 per cent. Among these malignant tumors we obtained a ratio for serous to pseudomucinous types of 3 to 1. Barzilai's<sup>7</sup> figure for this ratio is 2½ to 1. About one-third of our serous tumors were found to be malignant while only 1 of 8 pseudomucinous tumors were so classified. This latter ratio is much greater than Novak's<sup>4</sup> experience of 1 in 20.

Among a series of 1,268 dermoids, Meyer<sup>5</sup> found 1.7 per cent of them malignant. In this study, slightly less than 1 per cent proved to be so. No adequate figures have been found in the literature for the frequency of granulosa cell tumors or their malignant counterparts. We have found the incidence of granulosa cell tumors to be roughly 2 per cent of ovarian neoplasms, 30 per cent of which are malignant. Dockerty<sup>3</sup> states that clinical recurrences and metastases vary in different reports from 4.5 per cent to 33 per cent.

### Background of Patients

Of the total number of patients, 12.5 per cent gave a history of malignancy in their family. Montgomery,<sup>9</sup> in a recent article, found this figure to be 13.5 per cent. Ten per cent of our cases had a family history of tuberculosis while 3 per cent had had diabetes.

It may be noted that sixty (22.6 per cent) of our 265 cases had had gynecological operations in their past, fifty of these procedures having been for benign conditions and ten for malignancy of various types. Among the latter there were two breast carcinomas, two carcinomas of the cervix, one case of carcinoma of the endometrium and five cases of ovarian malignancy. The latter were composed of cases which either had been operated upon and considered hopeless or in which the other ovary had been removed years previously for malignancy. Ten of the cases had received radiation for benign bleeding or for some of the malignancies already mentioned.

### Age Distribution

Table II shows the number of cases occurring in each decade of life. As one might expect, for most malignancies, nearly 59 per cent of the patients were between the ages of 40 and 60 years at the time they appeared for treatment. The youngest patient was 23 and the oldest was 86. There were seven patients under the age of 30 while four were over 80. Patients with pseudomucinous carcinoma showed no significant age difference from those having the serous type although it is generally believed that pseudomucinous cysts arise after the menopause in only 10 per cent of women so afflicted. This would suggest that such cysts lie dormant for long periods of time before becoming malignant.

It seemed interesting to us that two of the three malignant dermoids occurred in the 70- to 80-year age group. It is generally thought that dysgerminomas occur in the younger age groups, but one of ours was in her fourth decade and the other in her sixth.

Premenopausal patients represented 39 per cent of the total cases while 61 per cent were in the postmenopausal period. It is interesting to note that 43 per cent of the premenopausal group were alive five years following treatment but that only 28 per cent of the postmenopausal patients lived that long. The factor of more advanced age in the latter group does not fully explain this difference in salvageability. Therefore, older patients apparently have more malignant tumors.

TABLE II. AGE DISTRIBUTION

AGE GROUP	NUMBER OF CASES
20-29	7
30-39	27
40-49	75
50-59	80
60-69	54
70-79	18
80-89	4
Total	265



### Marital Status

Married patients comprised 81.6 per cent of the total and 31.5 per cent of them had not had any term pregnancies. Wharton<sup>10</sup> states that about 10 per cent of married couples are sterile. Other estimates run around 15 per cent. Dockerty,<sup>3</sup> in his extensive review, indicates that 40 per cent of women with ovarian cancer are sterile. Thus, our figures tend to agree that patients suffering from cancer of the ovary are less fertile as a group. There was, however, no significant deviation among the various tumor types with respect to this infertility.

### Symptomatology

Enumeration and relative frequency of various symptoms are shown in Table III. None of these symptoms are very specific. As in most other studies of ovarian cancer, low abdominal pain and abdominal enlargement are the preponderating symptoms. When the symptom of pain was plotted against prognosis, it was found that cases with this complaint had neither better nor worse five-year salvage figures.

TABLE III. SYMPTOMS

SYMPTOM	NUMBER OF CASES	PER CENT OF CASES
Low abdominal pain	143	53.9
Abdominal enlargement	142	53.5
Gastrointestinal complaints	57	21.5
Genitourinary complaints	53	20.0
Abnormal vaginal bleeding	49	18.5
Pelvic pressure	46	17.4
Backache	36	13.5

The figure of 18.5 per cent for abnormal vaginal bleeding has been corrected for causes probably unrelated to the ovarian cancer such as endometrial hyperplasia, fibroids, and primary associated endometrial carcinoma. Meigs<sup>11</sup> reported 30 per cent of ovarian malignancies as having abnormal bleeding but it is not stated whether his figures were corrected in this manner.

Of the 49 cases with vaginal bleeding (excluding the probable unrelated causes enumerated above), thirteen were most likely due to the occurrence of endometrial metastasis. This leaves a balance of 37 cases wherein the cause of bleeding is unknown but may possibly be explained on the basis of generally hyperactive ovarian stroma.

The incidence of abnormal vaginal bleeding was the same for both the premenopausal and postmenopausal groups.

When the duration of symptoms was plotted against five-year salvage (Table IV), it was found that those cases having symptoms longer than six months had a slightly better prognosis. Again, when the duration of symptoms was compared with the number of cases presenting metastasis (Table IV), it was seen that the patients having symptoms of less than six months had a considerably higher metastatic rate. At first glance it would seem that the reverse of these situations should be true, i.e., the longer the patient played host to a tumor, the greater the chance for metastasis to develop and the poorer the prognosis would be. We explain this paradox by postulating that cases with shorter duration of symptoms had a more fulminating type of lesion.

TABLE IV. DURATION OF SYMPTOMS VS. PROGNOSIS AND METASTASIS

DURATION	NUMBER OF CASES	FIVE-YEAR SALVAGE		METASTASES	
		NUMBER	PER CENT	NUMBER	PER CENT
Three months	69	23	33.3	41	59.4
Six months	57	20	35.1	33	57.9
Six months plus	100	37	37.0	47	47.0
Total	226*	80	35.4	121	53.5

\*The duration of symptoms was not clear in all cases. In other cases a five-year follow-up was not available.

### Physical Signs

The relative incidence of the more important physical signs is shown in Table V. According to expectations, pelvic and abdominal masses occurred with great frequency. When the signs were distributed among the various tumor types of the primary classification, no statistically significant variation was found.

Ascites was tabulated whether it was found preoperatively or at operation. We found this sign in approximately 31 per cent of all cases and in 36 per cent of cases having a solid tumor. Geist<sup>12</sup> and Meigs<sup>11</sup> each quote a figure of 50 per cent for ascites in association with solid tumors. When we considered ascites as a prognostic factor, we discovered that 21 per cent of patients showing this sign were alive at five years; this is much lower than the over-all rate of 35 per cent.

TABLE V. PHYSICAL SIGNS

SIGN	NUMBER OF CASES	PER CENT
Pelvic mass	230	86.8
Abdominal mass	203	76.6
Ascites	82	30.9
Weight loss	75	28.3

### Pathology

The punch-card system has been extremely useful for correlating pathological attributes of various types of ovarian carcinomas with each other and with their clinical features. Microscopic types, gross types, grading and papillarity are discussed separately and comparatively.

Our primary break-down of cases is shown in Table VI. The usual microscopic designations of type were used with the exception of an undifferentiated group which is composed of those cases we could not honestly classify and the endometriocarcinomas. The endometriocarcinomas include those cases in which we felt sure the carcinoma had arisen in a pre-existing endometrioma. In this connection, Smith<sup>13</sup> estimated that 22 per cent of the better-differentiated ovarian carcinomas were either associated with, or related to, endometriosis.

TABLE VI. CLASSIFICATION

MICROSCOPIC TYPE	NUMBER OF CASES	PER CENT OF CASES
Serous cystadenocarcinoma	160	60.3
Pseudomucinous cystadenocarcinoma	54	20.3
Undifferentiated adenocarcinoma	24	9.1
Granulosa cell carcinoma	11	4.2
Malignant dermoid	3	1.1
Hypernephroma (Grawitz tumor)	6	2.3
Dysgerminoma	2	0.8
Endometriocarcinoma	3	1.1
Carcinosarcoma	2	0.8
Total	265	100.0

#### A. Primary Classification and Its Relationships.—

(1) *Bilateral Tumors:* The incidence of bilateral ovarian carcinomas, as determined at the first operation, is shown in Table VII. The total occurrence of 32 per cent seems low when compared with other series. Montgomery,<sup>9</sup> in a recent review of 87 cases, showed a 70 per cent bilaterality. This difference may be explained, in part, by a greater number of advanced cases in his series.

Pseudomucinous carcinomas are least likely to be bilateral (15 per cent) and the undifferentiated types most likely to be so (50 per cent) while the serous group occupies an intermediate position with 37 per cent.

TABLE VII. BILATERAL TUMORS

CLASSIFICATION	NUMBER OF CASES	PER CENT OF CASES WITH BILATERAL TUMORS
Serous	160	36.9
Pseudomucinous	54	14.8
Undifferentiated	24	50.0
Granulosa cell carcinoma	11	27.3
Malignant dermoid	3	0.
Hypernephroma	6	16.7
Miscellaneous*	7	42.8
Total	265	32.1

\*See Table VI for identity of these tumors.

(2) *Size of Tumors:* The size of the tumor (or of the ovary containing the tumor) was recorded in 255 cases. Size was classified as small (up to 5 cm.), medium (5 to 15 cm.), and large (15 cm. or more). Thus it may be seen from Table VIII that 60 per cent of all the tumors fell into the maximum-sized category, while only 5 per cent were under 5 cm. The majority of tumors possess a fairly large mass, which fact may be of considerable clinical importance.

When the primary break-down is used for comparative purposes, the pseudomucinous group contains a huge majority (81 per cent) of large tumors while the serous group has a smaller majority (56 per cent) of maximum-sized tumors. The undifferentiated tumors average somewhat less by comparison. The granulosa cell carcinomas are preponderantly medium-sized tumors, which is consistent with the smaller size of their benign counterparts.

TABLE VIII. SIZE OF TUMORS

CLASSIFICATION	PER CENT OF CASES WITH		
	SMALL TUMORS	MEDIUM TUMORS	LARGE TUMORS
Serous	3.9	39.9	56.2
Pseudomucinous	1.9	17.0	81.1
Undifferentiated	13.0	39.1	47.9
Granulosa cell carcinoma	18.1	45.5	36.4
Malignant dermoid	0.0	0.0	100.0
Miscellaneous	8.3	41.7	50.0
	5.1	34.9	60.0

(3) *Contents of Cysts:* The type of fluid present in the cystic portions of the tumors was described in 156 cases. There were a considerable number of cysts which contained blood in addition to other fluids. This was probably due to operative trauma in many cases but may represent a close relationship to endometriosis or even indicate that the malignant process arose in an endometrioma.

A majority of the serous cysts contained serous fluid, but 28 per cent contained pseudomucinous material as well. Although 83 per cent of the pseudomucinous cysts showed fluid characteristic of their type, it is notable that 26 per cent of them contained serous fluid also.

Because of the presence of more than one type of fluid in a cystic tumor, it must be concluded that a reliable diagnosis of histologic type cannot invariably be made upon consideration of the fluid alone.

(4) *Grading:* Table IX shows the relationship of microscopic type to grading in 239 cases. Grade I tumors comprised 29 per cent of the total while Grade II and Grade III were 38 per cent and 33 per cent, respectively. When the more malignant tumors (Grade II and Grade III) were considered, a percentage of 71 was obtained. This figure agrees rather closely with Montgomery<sup>9</sup> whose Grade II and Grade III cases totaled 73.5 per cent.

It is evident that the undifferentiated tumors are the most malignant, for 96 per cent of them fall into Grades II and III with 78 per cent in the latter grade. The pseudomucinous group, on the other hand, is the least malignant, as 94 per cent of it is relegated to the Grade I and Grade II classifications. The serous carcinomas occupy a position intermediate to the above groups with 73 per cent of their number falling into Grades II and III. Thus an order of malignancy can be established for the main tumor types. (The granulosa cell carcinomas were not graded and the miscellaneous types were too few in number to be of any statistical significance.)

TABLE IX. RELATION OF MICROSCOPIC CLASSIFICATION TO GRADING

CLASSIFICATION	NUMBER OF CASES	PER CENT OF CASES		
		GRADE I	GRADE II	GRADE III
Serous	156	27	39	34
Pseudomucinous	52	46	48	6
Undifferentiated	23	4	18	78
Malignant dermoid	2	50	0	50
Hypernephroma	3	33	33	33
Carcinosarcoma	2	0	0	100
Endometriocarcinoma	1	0	0	100
	239*	29	38	33

\*In some categories, notably granulosa cell carcinoma, grading was not done in all cases. A sufficient number were graded, however, to obtain a fair sampling of morphologic variants.

(5) *Metastasis*: It appears that tumors showing metastasis at operation are more malignant than those without. This belief arises from the fact that only 21 per cent of patients having metastasis lived for five years while the over-all salvage at five years is 35 per cent.

TABLE X. METASTASES

CLASSIFICATION	TOTAL CASES	CASES WITH METASTASES		LOCATION OF METASTASES		
		NUMBER	PER CENT	PER CENT OF METASTASES IN		
				PELVIS	ABDOMEN	UTERUS
Serous	160	89	56	87	64	8
Pseudomucinous	54	21	40	57	71	38
Undifferentiated	24	17	71	94	77	18
Granulosa cell carcinoma	11	5	45	60	60	0
Malignant dermoid	3	1	33	100	0	0
Hypernephroma	6	1	17	100	0	100
Endometriocarcinoma	3	0	0	0	0	0
Dysgerminoma	2	2	100	100	50	0
Carcinosarcoma	2	1	50	100	100	0
	265	137	52	82	66	14
Total pelvic metastases		113	(43 per cent of all cases)			
Total abdominal metastases		90	(34 per cent of all cases)			
Total uterine metastases		19	(7 per cent of all cases)			

Metastasis had occurred in 52 per cent of the 265 cases at the time of operation (Table X). The pelvic cavity was the most frequent site of metastasis (82 per cent), but 66 per cent of the metastases were found in the abdominal cavity and 14 per cent in the uterus, chiefly in the endometrium. The overlap in percentages is accounted for by the fact that many cases had both abdominal and pelvic metastases while several had them in the endometrium as well. When the frequencies of metastatic site are compared to the total number of cases (265), it is found that 43 per cent of the cases had pelvic metastases, 34 per cent had metastases in the abdominal cavity, and 7.2 per cent in the uterus.

Serous carcinomas tended more to pelvic metastasis, while pseudomucinous types tended more to the abdominal cavity. Pseudomucinous tumors metastasized to the endometrium in a surprising number of instances, namely, in 8 of 21 cases.



If it can be assumed that metastasis is an indication of greater malignancy of a tumor type, it follows that the undifferentiated group is the most malignant since 71 per cent of its number metastasized. Next in order are: serous, 56 per cent; granulosa cell carcinoma, 45 per cent; and pseudomucinous, 40 per cent. This is the same order of malignancy that was obtained by grading.

(6) *Salvage Rates (Prognosis)*: Table XI gives the five-year salvage rates for all cases in our primary classification (26 cases had not been followed long enough). There is close agreement between prognosis and the order of malignancy previously established by grading and metastasis. The exception to this conclusion is the granulosa cell group, none of which was alive at the end of five years.

TABLE XI. COMPARISON OF SALVAGE RATES BY HISTOLOGICAL CLASSIFICATION

CLASSIFICATION	NUMBER OF CASES	ALIVE AT 5 YEARS	
		NUMBER	PER CENT
Serous	143	51	35.7
Pseudomucinous	51	24	47.1
Undifferentiated	22	4	18.2
Granulosa cell carcinoma	10	0	.0
Hypernephroma	4	1	25.0
Malignant dermoid	2	0	.0
Dysgerminoma	2	0	.0
Endometriocarcinoma	3	3	100.0
Carcinosarcoma	2	0	.0
	239	83	34.7

### Gross Pathology and Its Relationships

All tumors were divided into a gross classification of (a) cystic, (b) semi-solid (partly cystic tumors with solid areas of at least 2 cm. in diameter), and (c) solid. The latter group was predominantly solid although a few had small areas of cystic degeneration. The incidence of these gross types is shown in Table XII where it is seen that a large percentage of the pseudomucinous tumors are grossly cystic and the undifferentiated tumors are preponderantly of the solid variety. Here again, the serous and granulosa cell types, although showing a large percentage of semisolid and solid tumors, fall into an intermediate position. It is clinically important to note that 69 per cent of ovarian carcinomas contain solid areas of two centimeters or more.

TABLE XII. GROSS CLASSIFICATION

MICROSCOPIC TYPE	GROSS TYPE PER CENT		
	CYSTIC	SEMI-SOLID	SOLID
Serous	26	68	8
Pseudomucinous	61	35	4
Undifferentiated	4	22	74
Granulosa cell carcinoma	20	70	10
Miscellaneous	22	64	14
	31	55	14

By determining the relative position of these gross types with regard to grading (Table XIII), metastasis (Table XIV), and prognosis (Table XV), we have attempted to prove that the completely cystic tumors are the least malignant and the semi-solid and solid types are progressively more so.

TABLE XIII. RELATION OF GROSS TYPE TO GRADING

GROSS TYPE	GRADE I PER CENT	GRADE II PER CENT	GRADE III PER CENT
Cystic	55	36	9
Semisolid	21	42	37
Solid	0	27	73

TABLE XIV. RELATION OF GROSS TYPE TO METASTASIS

GROSS TYPE	NUMBER OF CASES	METASTASES	
		NUMBER	PER CENT
Cystic	80	25	31.2
Semisolid	138	81	58.7
Solid	35	30	85.7

TABLE XV. RELATION OF GROSS TYPE TO PROGNOSIS

GROSS TYPE	NUMBER OF CASES	ALIVE AT 5 YEARS	
		NUMBER	PER CENT
Cystic	74	43	58.1
Semisolid	130	38	29.2
Solid	28	5	17.8

### Significance of Papillae

It is well known that a large number of proliferative ovarian cysts, both benign and malignant, contain papillae. We have attempted to determine whether tumors presenting gross papillae are more or less malignant than those without such protrusions by comparing papillary tumors with gross type, grading, and prognosis. Further breakdown was made by dividing papillae into inverting and everting types.

Apart from the fact that 74 per cent of the malignant tumors showed papillae, of both inverting and everting types, no conclusions could be drawn as to their significance with regard to degree of malignancy.

### Grading

Grading has been used in this study as a factor in determining the degree of malignancy. In Tables XVI, XVII, and XVIII, we have used the factors of metastasis, prognosis, and radiation response as a check on the reliability of the grading procedure.

In proceeding from Grade I to Grade III, it may be noted that the metastatic rate rises from 31 per cent to 74 per cent. An inverse relation exists for five-year salvage: 65 per cent for Grade I tumors down to 7 per cent for Grade III.

TABLE XVI. RELATION OF GRADING TO METASTASIS

GRADING	NUMBER OF CASES	METASTASES	
		NUMBER	PER CENT
Grade I	71	22	31.0
Grade II	92	50	54.3
Grade III	82	61	74.4
	245	133	54.2

\*TABLE XVII. RELATION OF GRADING TO PROGNOSIS

GRADING	NUMBER OF CASES	FIVE-YEAR SALVAGE	
		NUMBER	PER CENT
Grade I	63	41	65.1
Grade II	91	34	37.4
Grade III	69	5	7.2
	223	80	35.9

In general, the more anaplastic a tumor, the greater the susceptibility to radiation. This is rather well borne out in Table XVIII where the percentage of improvement with added x-ray advances from 31 per cent for Grade I tumors to 850 per cent for Grade III tumors. Incidentally, it may be seen from this same chart that x-ray added to surgery improves the five-year salvage by 69 per cent.

TABLE XVIII. RELATION OF GRADING TO RADIATION RESPONSE

GRADING	PER CENT FIVE-YEAR SALVAGE		PER CENT IMPROVEMENT
	SURGERY ALONE	SURGERY AND X-RAY	
Grade I	58	76	31
Grade II	32	47	47
Grade III	2	19	850

### Associated Pathology

Table XIX shows the incidence of the accompanying types of pathology. All this pathology was located in the pelvis with the exception of five cases of colonic carcinoma, some of which were partly within the pelvis, and two cases of breast cancer. The percentage (11 per cent) of associated benign ovarian tumor may seem surprising, although Smith<sup>13</sup> noted that 23 per cent of all proliferative ovarian tumors showed two or more types of primary new growth. This multicentric tendency may also account for the occurrence of three cases of multiple primary carcinoma of the ovary in our series.

TABLE XIX. ASSOCIATED PATHOLOGY

	NUMBER OF CASES	PER CENT OF CASES
Other primary cancers	21	7.9
Benign ovarian tumors	28	10.6
Fibroids	90	34.0
Pelvic inflammation	71	26.8
Endometrial hyperplasia	34	12.8
Endometriosis and adenomyosis	31	11.7

The occurrence rate of associated uterine fibroids (34 per cent) is somewhat higher than the attack rate for this type of tumor in noncancerous women. Novak<sup>4</sup> and Wharton,<sup>10</sup> respectively, state this rate to be 20 per cent and 26 per cent in women over age 30.

The cases having chronic salpingitis were not divided into primary and secondary types of inflammation so that little can be deduced from them as possible etiologic agents.

Endometrial hyperplasia occurred in 13 per cent of our cases. This figure may seem rather high for a female population of this age group, but it must be realized that one-third of these hyperplasias occurred in cases of granulosa cell carcinoma, all of which showed this condition.

Endometriosis and adenomyosis have been grouped together and show an incidence of 11.7 per cent. A large proportion of these cases had endometriosis of the external type and, in 20 cases (7.6 per cent of our entire series), this was located in an ovary on the involved or opposite side.

### Multiple Primary Carcinoma

Twenty-one (8.3 per cent) of the 265 cases herein presented had multiple primary cancer. Two of these cases had three separate primary sources of the disease, one showing adenocarcinoma of the endometrium and of the colon in addition to the ovarian carcinoma. Another case presented a separate adenocarcinoma of the endometrium and a small but definite sarcoma located but a few millimeters from the ovarian carcinoma.

In eleven of the twenty-one cases, the other primary malignancy arose in the endometrium. There were three cases in which the different cancer type was located in the same or other ovary. The remainder of the multiple primary foci were in the colon (five instances), cervix (two instances), and breast (two cases). In some instances the additional neoplasms had existed prior to the discovery of the ovarian lesion while some were discovered at follow-up operations.

### Results of Treatment

Only the 239 cases which were followed for at least five years are considered in this section. All of the cases were operated upon by various members of the staff through the years. Although, at the time of this study, it was impossible to ascertain the intentions of the various operators, it seems to have been the policy to remove as much of the growth and as many of the pelvic organs as possible, at times seemingly without regard for the apparent hopelessness of the situation. This fact may have been of importance in the five-year salvage figures which are somewhat above the average quoted by most authors.

For a time it was considered wise to perform an excision of the omentum routinely but an analysis of these cases showed no improvement in salvage figures. Before the advent of x-ray therapy, the use of lead had some vogue in the post-operative treatment of a number of these cases. It has been impossible to attribute any favorable effect on prognosis to this method of treatment. Radium was used on a few patients with similarly negligible results.

Since 1930 many cases have been treated with deep x-ray therapy in addition to the usual surgical procedures. Eighty-five such cases are reported at this time. The dose has varied from 3,000 to 9,000 r. and some of the patients did not complete the recommended number of treatments. There is no discernible reason why some patients were selected for this form of therapy. However, at the present time it is a general rule that all patients with ovarian carcinoma receive x-radiation in addition to surgery.

Table XX shows the disposition of all patients at the end of five years. It should be noted that our over-all five-year salvage figure of 35 per cent has not been corrected for postoperative deaths, deaths from intercurrent disease, or for those patients who became untraceable before five years had elapsed. In other words, all patients dead or untraceable at the end of five years were counted as cancer deaths. On the other hand, it was known that a few of the patients alive at the end of five years still had incurable cancer.

TABLE XX. COMPARISON OF SALVAGE RATES BY HISTOLOGICAL CLASSIFICATION

CLASSIFICATION	NUMBER OF CASES	POST- OPERA- TIVE DEATHS	DEAD OF OTHER DIS- EASES	DEAD OF CAR- CINOMA	UN- TRACED	ALIVE AT FIVE YEARS	
						NUMBER	PER CENT
Serous	143	10	6	62	14	51	35.7
Pseudomucinous	51	1	1	21	4	24	47.1
Undifferentiated	22	3	1	13	1	4	18.2
Granulosa cell	10	0	1	7	2	0	.0
Hypernephroma	4	0	0	2	1	1	25.0
Dermoid	2	0	1	1	0	0	.0
Dysgerminoma	2	0	0	2	0	0	.0
Endometriocarcinoma	3	0	0	0	0	3	100.0
Carcinosarcoma	2	0	0	2	0	0	.0
	239	14	10	110	22	83	34.7

The operative mortality rate was 5.9 per cent (14 deaths occurring within 40 days from the time of operation). The fact that ten of these deaths occurred in the decade 1933 to 1942 does not correlate very well with the generally improved surgery of that period. Four per cent of the patients died of intercurrent disease during the first five-year follow-up period while 9 per cent were lost. At the end of these first five years, 46 per cent of the total patients were dead from progressive or recurrent cancer, most of these dying within two years of operation. This left 83 living patients or an over-all five-year salvage figure of 35 per cent. The latter figure is higher than Meig's<sup>11</sup> 15 per cent, Mont-



gomery's<sup>9</sup> 20.5 per cent, and an early series of Taylor's,<sup>16</sup> 15 per cent. Taylor<sup>2</sup> reported a later series, however, which included patients treated with x-ray, in which his over-all salvage for five years was 35 per cent.

Table XXI shows the long-time follow-up of the 239 patients, giving the per cent alive at the end of each successive five-year interval. Age and inter-current disease took the largest toll of these patients after their first five years of follow-up although definite recurrences were noted after the following intervals: twenty years (2 cases), seventeen years, nine years (2 cases), eight and one-half years, and five years.

TABLE XXI. LONG-RANGE FOLLOW-UP OF ALL PATIENTS

PERIOD	NUMBER OF CASES	PER CENT ALIVE AT FIVE-YEAR INTERVALS					
		5 YEARS	10 YEARS	15 YEARS	20 YEARS	25 YEARS	30 YEARS
1903-1912	18	28	22	22	6	6	0
1913-1917	17	18	6	6	6	6	6
1918-1922	18	33	33	22	11	0	
1923-1927	37	38	27	16	6		
1928-1932	40	30	20	8			
1933-1937	53	42	30				
1938-1942	56	38					
	239	35	25	14	7	4	3

Table XXII compares the results from surgery alone with those from surgery plus x-ray over a fifteen-year follow-up span. It is interesting that the results from added x-ray show considerable improvement in the five- and ten-year salvage rates but that at fifteen years the figures are identical. This tends to confirm observations by Pemberton<sup>1</sup> and others that radiation therapy increases longevity and comfort of the patient but does not necessarily cure the disease. The results from surgery alone appear more unfavorable than they really are when compared to those cases receiving x-ray since all the postoperative deaths are absorbed in the former group. When a correction factor for this is introduced, however, the results of the cases x-rayed are still 12 percentage points better than with surgery alone.

TABLE XXII. COMPARISON OF SURGERY TO SURGERY AND X-RAY

INTERVAL	PER CENT ALIVE AT FIVE YEARS		
	SURGERY	SURGERY AND X-RAY	COMBINED
5 years	29	46	35
10 years	20	36	25
15 years	14	14	14

TABLE XXIII. COMPARATIVE RESULTS OF VARIOUS OPERATIVE PROCEDURES

OPERATION	SURGERY ALONE		SURGERY AND X-RAY		COMBINED TREATMENT	
	NUMBER	PER CENT ALIVE AT 5 YEARS	NUMBER	PER CENT ALIVE AT 5 YEARS	NUMBER	PER CENT ALIVE AT 5 YEARS
Exploratory and/or biopsy	12	8.3	6	0.0	18	5.5
Oophorectomy	38	13.2	15	33.3	53	19.0
Supravaginal hysterectomy and oophorectomy	89	38.2	47	48.9	136	42.0
Complete hysterectomy and oophorectomy	15	26.6	17	64.7	32	47.0
	154	29.0	85	45.9	239	35.0

Table XXIII compares the results of various operations, with and without x-ray. The exploratory type of operation naturally carried the poorest prognosis for these patients had such extensive disease and metastasis as to preclude any attempt at removal. This same hopeless situation often prevailed in cases where oophorectomy alone was done. In all but a few cases where hysterectomy was performed, bilateral oophorectomy was also accomplished. There is very little statistical difference between the results from the supravaginal and those from the complete type of hysterectomy. The relatively small number of the latter is but an indication of the more recent trend toward complete hysterectomy.

### Summary and Conclusions

1. During a period of 43 years, 1,740 proliferative ovarian tumors were found at the Free Hospital for Women. Of these tumors, 265 were malignant.
2. The incidence of benign and malignant types found in this clinic compares favorably with that of several authorities.
3. History of malignancy in the family occurred in 12.5 per cent of the patients.
4. In their past histories, 22.6 per cent of the patients had had gynecological operations, 9 of which were for various other malignancies.
5. The ages of the patients were distributed according to the usual expectancy for cancer; 59 per cent of them were between the ages of 40 and 60. The prognosis for premenopausal patients is much better than for postmenopausal, despite correction for the age factor.
6. Sterility occurred in 31.5 per cent of the patients.
7. The symptoms of ovarian carcinoma are not very specific. Lower abdominal pain and abdominal enlargement each occurred in 54 per cent of the cases.
8. Patients with short duration of symptoms (under six months) had a less favorable prognosis and a considerably higher metastatic rate.
9. Pelvic and abdominal masses occurred with great frequency. Ascites was present in 31 per cent of all cases and in 36 per cent of cases having a solid tumor. Ascites connotes a poorer prognosis.
10. Ovarian carcinoma occurred bilaterally in 32 per cent of the cases. Pseudomucinous carcinomas were bilateral in 15 per cent and the serous type in 37 per cent of the cases.
11. Only 5 per cent of the tumors measured 5 cm. or less, and 60 per cent of them were 15 cm. or more in diameter. Pseudomucinous tumors were large in 81 per cent of the patients.
12. The cyst contents showed considerable admixture of various types of fluid, and, therefore, a completely reliable diagnosis cannot be made on the type of fluid alone.
13. The order of malignancy for the various tumor types, as judged by grading, rate of metastasis, and salvage rates, is granulosa tumor, undifferentiated tumors, serous and pseudomucinous carcinoma, the latter being least malignant.
14. Metastasis occurred in 52 per cent of all cases. Patients with metastasis had a poorer prognosis. Uterine metastasis had occurred in 7.3 per cent of the cases.

15. Ovarian carcinomas contained solid areas of at least 2 cm. in diameter in 69 per cent of the cases. Cystic, semisolid and solid tumor types were progressively more malignant, in that order, as judged by grading, metastasis, and prognosis.

16. Apart from the fact that 74 per cent of the malignant tumors showed inverting and everting papillae, no conclusions could be made as to their significance with regard to degree of malignancy.

17. Grading is a reliable and important procedure when checked against the factors of metastasis, prognosis, and radiation response.

18. In 8.3 per cent of the cases, more than one type of primary cancer was found at the time of operation or later in the follow-up. About one-half of these cancers were located in the endometrium.

19. The combined results of treatment of all types produced 35 per cent salvage at the end of their first five years; 46 per cent died of cancer, 4 per cent died of other diseases, 9 per cent were lost, and 5.9 per cent died as a result of the operation.

20. The results from surgery alone at the end of five-, ten-, and fifteen-year intervals were, respectively, 29 per cent, 20 per cent, and 14 per cent. The results from surgery with the addition of x-ray for the same intervals were 46 per cent, 36 per cent, and 14 per cent.

21. Recurrences have occurred as long as twenty years following operation. Seven recurrences were noted after five years.

22. The results from any operation other than hysterectomy and bilateral oophorectomy were negligible. The complete hysterectomy seemed to have a slight advantage over the supravaginal type.

Acknowledgment: The authors are indebted to N. Paul Isbell, M.D., and Paul Latour, M.D., for their assistance in reviewing the material herein presented, and to Mrs. Mabel C. Brown for her part in the production of this paper.

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## THE HISTOLOGIC APPEARANCE OF THE ENDOCERVIX DURING THE MENSTRUAL CYCLE\*

PAUL TOPKINS, M.D., F.A.C.S., BROOKLYN, N. Y.

*(From the Kings County Hospital, Department of Gynecology and Obstetrics)*

SINCE the work of Hitschmann and Adler, it has been established beyond dispute that the human endometrium undergoes characteristic cyclic changes during the ovulatory menstrual cycle. The study done by Novak and Everett<sup>1</sup> showed definitely that cyclic histologic variations also occur in the endosalpinx. The investigation made by Diercks<sup>2</sup> demonstrated certain cyclic changes in the vaginal mucosa. In regard to the latter, however, subsequent studies have yielded somewhat conflicting results (note the reports of Geist,<sup>3</sup> Traut, Bloch and Kuder,<sup>4</sup> and Zondek and Friedmann<sup>5</sup>). Zondek and Friedmann, for example, failed to find in the vaginal mucous membrane any changes comparable to those found in the endometrium. Their report maintained that in different parts of the vaginal mucosa varying microscopic pictures prevailed. This may be due to the nature of the embryologic development of the vagina, only part of which is supposed to be Müllerian in origin. In keeping with these genital tract findings, one would naturally be led to believe that the cervix, which, like the uterus and tubes, is entirely of Müllerian origin, must also undergo cyclic variations in its mucous membrane. The investigations of Wollner<sup>6, 7, 8</sup> and the work of Sjövall<sup>9</sup> indicated that such variations do exist. Although both Wollner and Sjövall found cyclic changes in the human endocervix, their descriptions, and consequently, their interpretations of those changes were entirely different.

This study was made to determine the nature of the histologic appearance of the endocervix during the menstrual cycle. Does the endocervix undergo cyclic histologic changes? If so, can these changes be correlated with those found in the endometrium?

### Procedure

The subjects for study were women in the reproductive period of life, normal physically and gynecologically, with histories of normal menstrual periods. They were selected from groups of postpartum patients who were not lactating, and who reported to the outpatient department immediately after the end of their first menstrual periods. These patients were examined, and those who had a vaginal discharge or cervical infection were discarded from the study. The patients who were retained for study returned at specified dates during subsequent menstrual cycles, at which times specimens of endometrium and endocervix were obtained concomitantly. For procuring

\*Thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, toward the requirements for the degree of Doctor of Medical Science (D.Sc.[Med.]) for graduate work in Gynecology and Obstetrics.



endometrium an ordinary semimalleable curette, which had been narrowed and sharpened, was used. For obtaining endocervix, a laryngeal punch on a universal handle was employed. This instrument yielded fairly good specimens of endocervix, much better than those which had previously been obtained with a very sharp, narrow curette. The endocervix, being so intimately a part of the underlying tissue, is not easily separated, and only after considerable practice was it possible to remove specimens good enough for study.

During a six-month period, eighty-six patients were utilized for the investigation. From them 420 biopsies were taken, 210 endometrial and 210 endocervical. Of these specimens, practically every endometrium was suitable for diagnosis. Owing to the difficulty of procuring good endocervical biopsies, however, only 150 specimens were considered acceptable for histologic study. Thus, a total of 300 biopsies was studied, 150 specimens of endocervix with their corresponding specimens of endometrium.

### Results

Of the 150 specimens of endometrium examined microscopically, approximately half were proliferative and half secretory. Histologically, they represented fairly evenly the various stages of development observed during the ovulatory menstrual cycle, from the earliest proliferative type seen at the end of flow, to the latest secretory pattern, found at the onset of menstruation. Almost always, the appearance of the endometrium coincided accurately with the picture one would expect to see at that particular time of the menstrual cycle. The few exceptions were those in which an early secretory endometrium was found at the end of the cycle.

The 150 specimens of endocervix presented a variety of histologic patterns, depending mainly upon the angle at which the tissue was sectioned. The lining epithelium, being continuous with that of the glands, showed the same differences and the same likeness as were found in the glandular epithelium. Thus, the epithelium of both lining and glands consisted of tall columnar cells, the height of which varied from slide to slide, and even on the same slide. Their basement membrane was almost always sharply defined. Their nuclei were dark, oval or spindle in shape, with their long axes parallel to those of the cells, except when compressed into disclike shapes against the basement membrane. The nuclei were usually located basally, sometimes centrally, occasionally toward the free surface. Frequently, where the lining was thrown into folds, or where the glands were invaginated into pseudopapillations, the nuclei were piled up irregularly. Now and then, all these types of nuclear arrangements could be seen in the same gland or in the intact lining membrane. The glands varied in size, some being much larger than others, even on the same slide. Thus, the number of glands in each field differed to a great degree. They also varied in shape, some being wide and short, others long and narrow. Some glands were round and of regular contour, whereas others were tortuous and irregular, some showing extremely numerous papillary excrescences. The latter appeared wherever the basement membrane was invaginated into the lumen of the gland. In the excrescences the superimposed cells often gave a "honeycomb" appearance, with their nuclei conglomerated far below into irregular tiers above the basement membrane. The papillary excrescences were interpreted, not as an expression of cellular proliferation, but rather, as a manifestation of uneven sectioning of compound racemose glands. This is demonstrated by observing a gland, in one segment of which the cells are arranged regularly, while in the opposite segment they are piled one on top of the other into a tuftlike projection. It would seem that proliferation, if it existed, would not be present in some part

of a gland and not in the rest of it. The amount of secretion from the gland cells varied, but some secretion could be seen under high magnification in most lumina. The extent of secretion was in no way related to the phase of the menstrual cycle, to the presence or absence of papillary excrescences, or to the position of the nuclei in relationship to the basement membrane. There was no evidence of denudation of the lining membrane during menstruation. The stroma consisted of dense connective tissue, among the fibers of which could be seen an occasional small blood vessel. The cell nuclei were usually quite large, mainly oval or spindle in shape, occasionally round, depending upon whether seen flatly or in profile. No evidence of congestion, edema, or devitalization of tissue was found. Mitotic figures could not be observed in the nuclei of the stromal or epithelial cells.

The foregoing description bore no relationship to the stage of the menstrual cycle as demonstrated in the corresponding endometrium. There were no endocervical findings characteristic of any stage of the cycle, under either low or high magnification. There was neither constancy of pattern nor consistency in detail at any given phase of the menstrual cycle. Thus, many endocervical biopsies were histologically similar, and yet their corresponding endometria revealed entirely different stages of development. Also, in many instances where endometrial biopsies were microscopically almost identical, their corresponding endocervices showed extreme differences in appearance. Finally, marked variations were frequently seen on the same slide of endocervix, at all periods of the menstrual cycle.

### Discussion

Evidence of a definite histologic cycle in the human endocervix was produced first by Wollner. Using a Hyams cervical electrode on a cutting current, he coned out specimens of endocervix during the course of the menstrual cycle. In his first investigation,<sup>6</sup> Wollner demonstrated a definite histologic cycle in six of the nine patients studied. In his second report,<sup>7</sup> consisting of fifty-four endocervical biopsies obtained from twenty women, a typical cycle was observed in eight patients. In some cases, however, premenstrual changes were found in the postmenstrual period. These reversed findings were interpreted by Wollner as an indication of hormonal imbalance. In his third study,<sup>8</sup> he correlated for the first time the histologic endometrial and endocervical variations. In a study of four cases, he confirmed his previous findings of definite cyclic changes in the endocervix.

During the postmenstrual phase, according to Wollner, the lining epithelium is low columnar, sharply outlined, with scanty cytoplasm, and nuclei close to the basement membrane. The glands are few in number, widely scattered, narrow, regular in contour, lined with moderately high columnar cells

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Fig. 1 (Case 24).—Early proliferative endometrium, taken three days after onset of menstruation. ( $\times 80$ .)

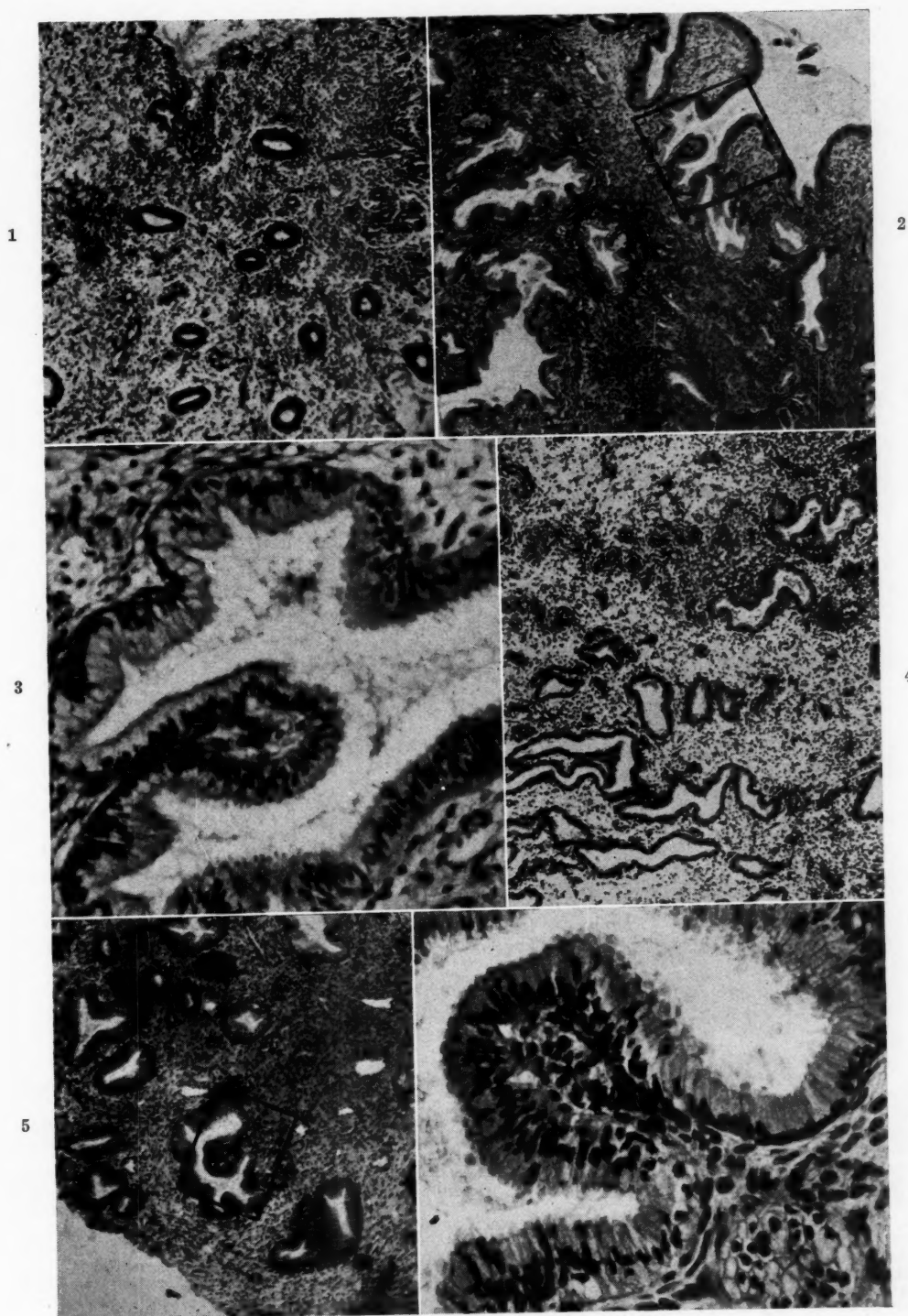
Fig. 2 (Case 24).—Endocervix, taken three days after onset of menstruation. Note the numerous glands, with papillary excrescences. Compare with Fig. 5, to which it is very similar. ( $\times 80$ .)

Fig. 3 (Case 24).—Endocervix, taken three days after onset of menstruation. Note the varying height of the gland cells and the different positions of their nuclei. Compare its similarity to Fig. 6. ( $\times 400$ .)

Fig. 4 (Case 34).—Late secretory endometrium, taken five days before the onset of menstruation. ( $\times 80$ .)

Fig. 5 (Case 34).—Endocervix, taken five days before onset of menstruation. Note the variation in gland architecture. Compare with Fig. 2. ( $\times 80$ .)

Fig. 6 (Case 34).—Endocervix, taken five days before the onset of flow. Note that the gland has been sectioned obliquely, the resulting superimposition of cells giving increased height to the epithelium. Compare with Fig. 3. ( $\times 400$ .)



*(See legends on opposite page.)*



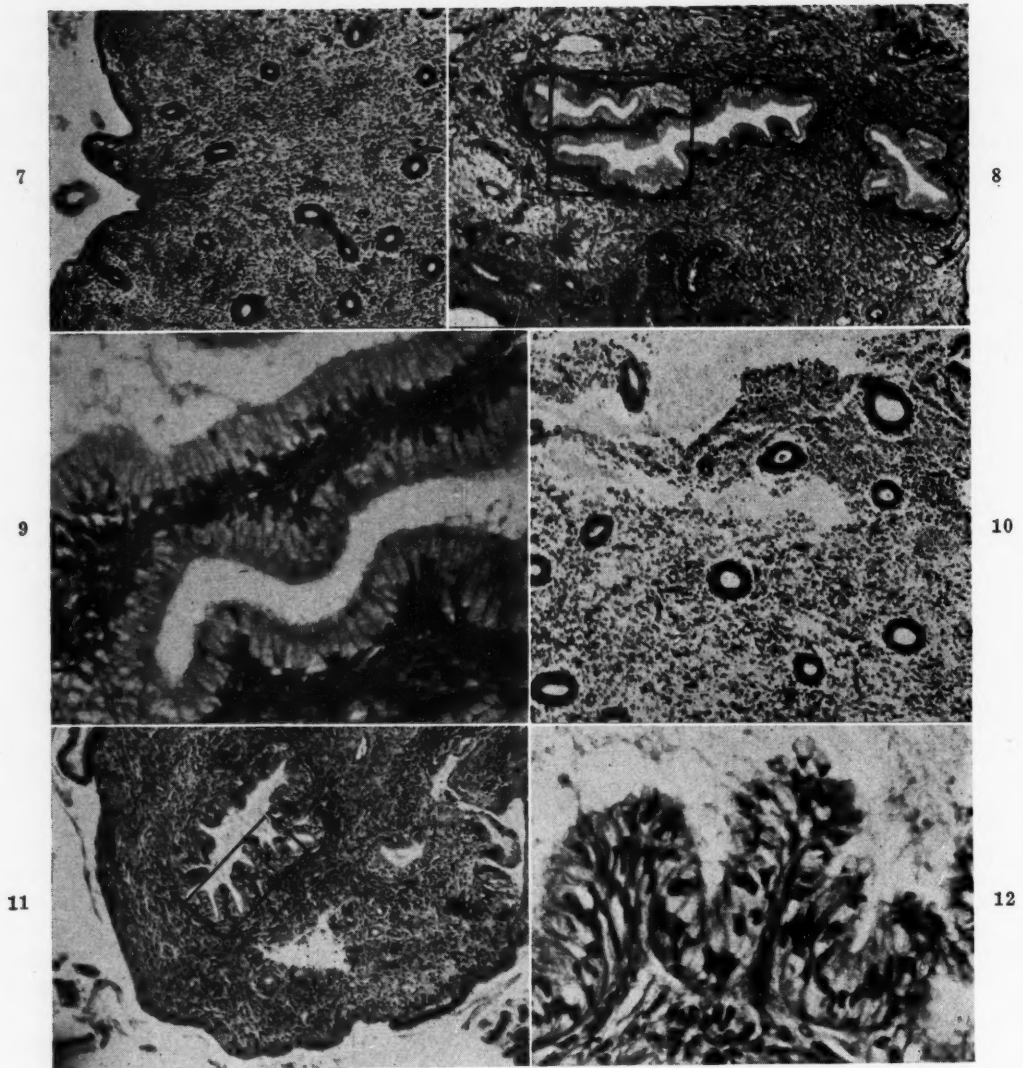


Fig. 7 (Case 38).—Early proliferative endometrium, taken four days after the onset of flow. ( $\times 80$ .)

Fig. 8 (Case 38).—Endocervix, taken four days after the onset of menstruation. Note the many excrescences, even at this very early period in the cycle. Observe its similarity to Fig. 17. ( $\times 80$ .)

Fig. 9 (Case 38).—Endocervix, taken four days after the onset of menstruation. Note how it differs from Fig. 12, although both specimens were taken at the same stage of the menstrual cycle. ( $\times 400$ .)

Fig. 10 (Case 66).—Early proliferative endometrium, taken seven days after onset of menstruation. ( $\times 80$ .)

Fig. 11 (Case 66).—Endocervix, taken seven days after onset of menstruation. Note that the nuclei in the gland are located basally, centrally, and irregularly, depending upon which segment is observed. ( $\times 80$ .)

Fig. 12 (Case 66).—Endocervix, taken six days after the onset of menstruation. Compare the tuftlike invagination of epithelial cells to that of Fig. 15. Note the irregularity in the size of the cells and in the shape of the nuclei owing to the angle at which the gland was sectioned. ( $\times 400$ .)



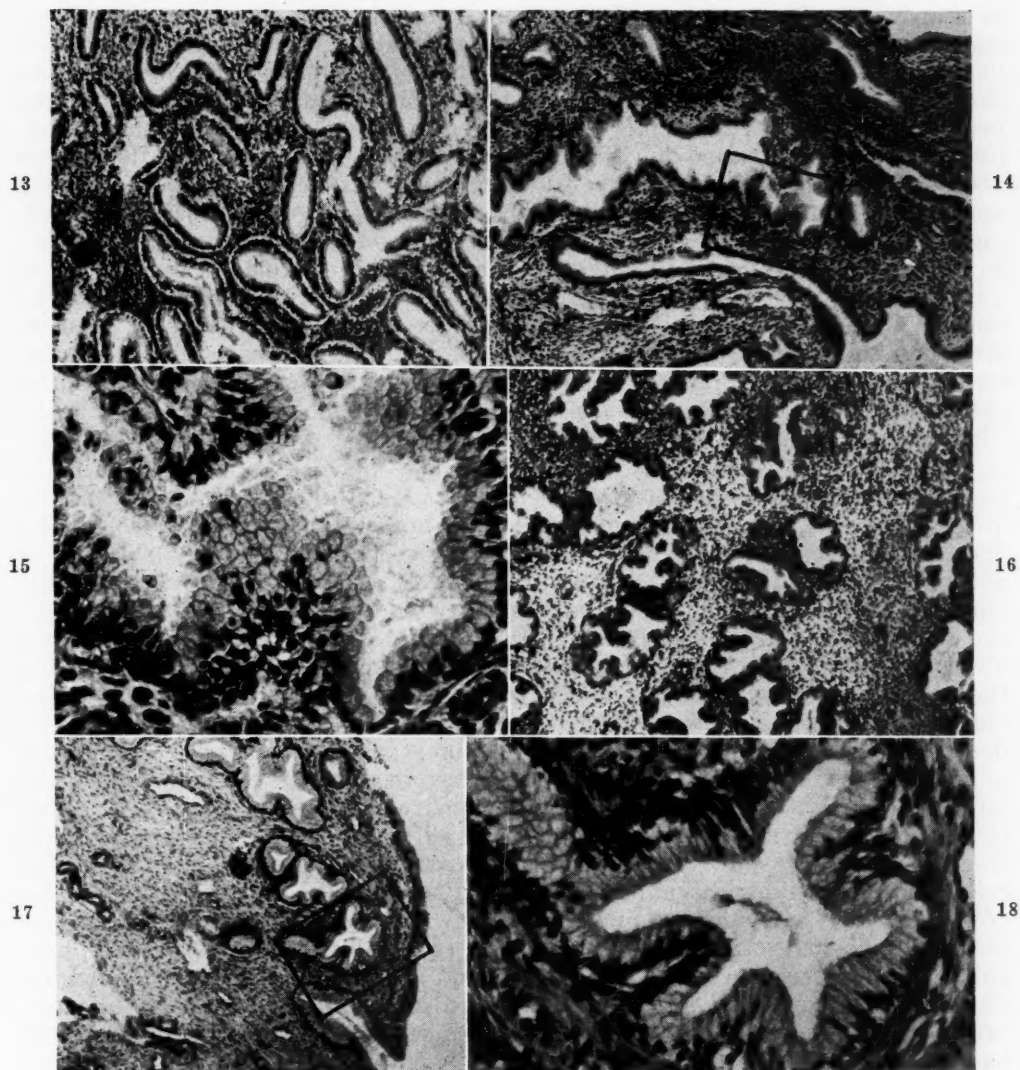


Fig. 13 (Case 17).—Early secretory endometrium, taken eight days before the onset of flow. ( $\times 80$ .)

Fig. 14 (Case 17).—Endocervix, taken eight days before the onset of menstruation. In the gland with the inset the nuclei are located basally, centrally, and in irregular tiers in the cell excrescences. ( $\times 80$ .)

Fig. 15 (Case 17).—Endocervix, taken eight days before the onset of menstruation. Note the juxtaposition of cells sectioned perpendicularly to their long axes, to give a "honeycomb" appearance. The tuftlike protrusion of cells in the upper part of the gland is similar to those seen in Fig. 12. ( $\times 400$ .)

Fig. 16 (Case 67).—Late secretory endometrium, taken at the onset of flow. Note the presence of edema and hemorrhage. ( $\times 80$ .)

Fig. 17 (Case 67).—Endocervix, taken at the onset of flow. Note the intact lining membrane, the absence of congestive changes or devitalization of tissue. Note its similarity to Fig. 8. ( $\times 80$ .)

Fig. 18 (Case 67).—Endocervix, taken at the onset of flow. Note its similarity to Fig. 9. ( $\times 400$ .)

whose nuclei are close to the basement membrane, with no evidence of secretion in the lumina. The stroma is dense and fibrous, with widely spaced cells of scanty cytoplasm, almost filled by small nuclei. The blood vessels are collapsed. During the course of the menstrual cycle there occur progressive qualitative and quantitative changes in these three mucosal elements, these changes culminating at the end of the premenstrual phase. At this time, just before menstruation, the lining cells are very high columnar, irregular in outline, with spindle-shaped nuclei crowded together. At this stage the glands are most numerous, are densely crowded, irregular, with profuse branching and papillation. They are much wider than before, and consist of high columnar cells bulging into the lumina, which now contain secretion. Owing to the increase in size and number of the glands, the stroma is diminished in quantity, but the stromal cells are larger and contain more cytoplasm. The blood vessels are engorged and edema is present. With the onset of menstruation there occurs extensive destruction of tissue, with complete denudation of the lining epithelium. Rapid regeneration follows, by proliferation of the glandular epithelium over the denuded surface, so that by the sixth day after the beginning of flow, epithelization is complete.

The work of Sjövall<sup>9</sup> also demonstrated cyclic histologic changes in the human endocervix, but of a different nature. He studied thirty-four cases, in different phases of the menstrual cycle, for correlation between endometrial and endocervical changes. The specimens were obtained by operation or autopsy. Although he stated that the glands vary in number, tortuosity, and length, depending upon the area from which the section was taken, how the specimen was cut, and from whom it was obtained, Sjövall nevertheless observed marked epithelial changes during the course of the cycle. During the early proliferative phase, beginning a few days after menstruation, the epithelium starts to grow. In numerous glands the cell multiplication is evidenced by the crowding of the nuclei, which in some places are markedly longer. At this stage gland papillation first begins to appear. During the late proliferative phase, although the intensity of reaction varies from case to case, proliferation of cervical glandular epithelium is pronounced. Everywhere the glands show irregular contours with extensive papillations. The cells are tall cylindrical and very densely arranged. In the papillary excrescences the band-shaped nuclei appear as dense brushes, in which some nuclei are pushed slightly ahead of others. During the early secretory phase epithelial proliferation is best developed, and it reaches excessive proportions. Papillation is now most marked. The gland surfaces and the basement membrane become more irregular, while the nuclei, although still located near the basement membrane, become very long and narrow. During the late secretory phase the papillations undergo gradual regression, until finally they almost disappear. Just prior to flow some specimens show a diminution in the number and extent of development of papillary excrescences, with shorter, more widely separated nuclei, while other specimens show a regression to an indifferent pattern, with papillations almost gone. Thus regression to the starting point is completed during the last part of the secretory phase, and results in the same picture that is seen at the beginning of the cycle. During menstruation the epithelium is fairly high, with round or short cylindrical nuclei located at the base of the cells and not very densely arranged. The epithelial outline is smooth and regular, and papillation is rare. Mucus is secreted throughout the entire cycle. The changes in the surface epithelium correspond to the cyclic changes found in the epithelium of the glands. There is no desquamation of the lining membrane during flow, nor any indication of active formation of new cells. The stroma, which during the proliferative phase is loose, vascular, and relatively cell poor, becomes during the late

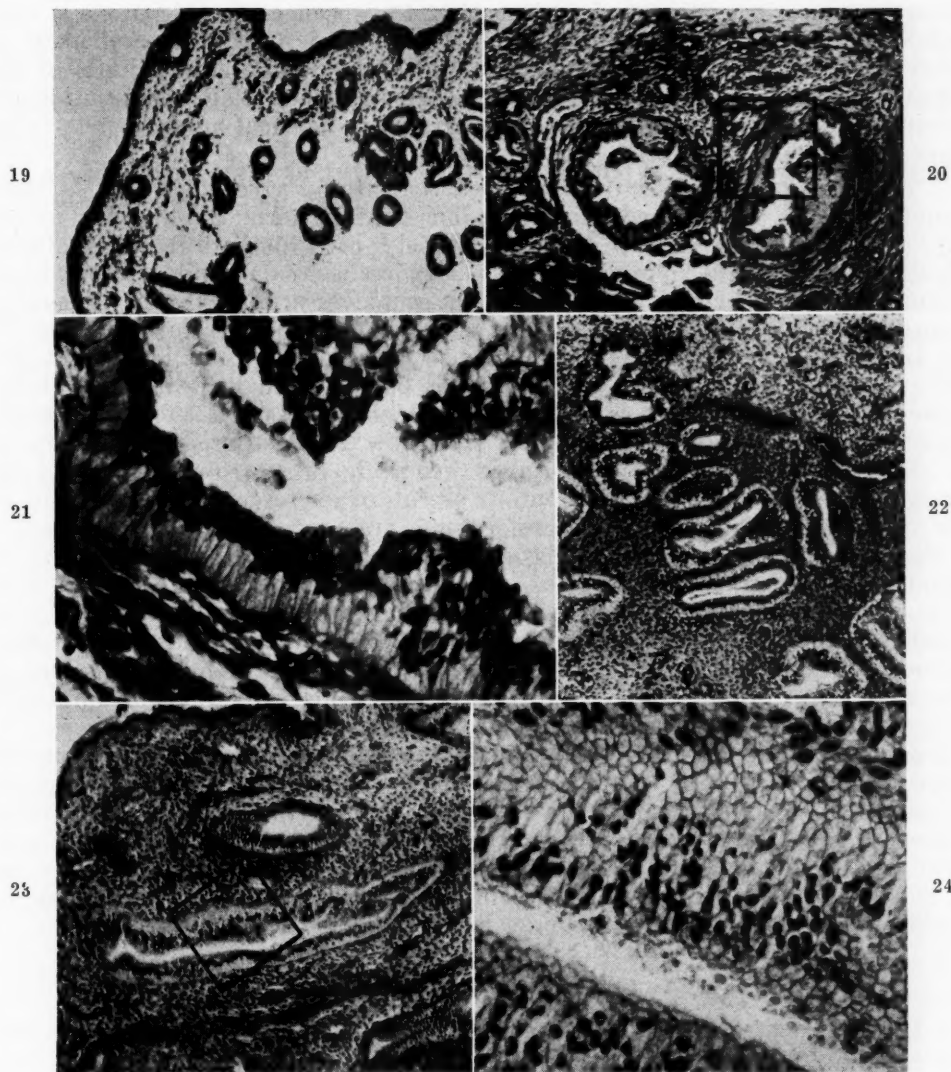


Fig. 19 (Case 87).—Early proliferative endometrium, taken eighteen weeks post partum during lactation amenorrhea. Onset of first menstruation two months later. ( $\times 80$ .)

Fig. 20 (Case 87).—Endocervix, taken eighteen weeks post partum during lactation amenorrhea, with a sharp curette. Note the piling up of cells and the location of the nuclei near their free margins in both lining and glands. Note the similarity to Fig. 23. ( $\times 80$ .)

Fig. 21 (Case 87).—Endocervix, taken eighteen weeks post partum during lactation amenorrhea. Note the "honeycomb" appearance of the cells in the papillation at the right upper angle of the photograph. Note its resemblance to Figs. 15 and 24. ( $\times 400$ .)

Fig. 22 (Case 58).—Early secretory endometrium, taken fourteen days before the onset of menstruation. ( $\times 80$ .)

Fig. 23 (Case 58).—Endocervix, taken fourteen days before the onset of flow. Note the absence of papillary excrescences. Also note the position of the nuclei in lining and gland cells. Compare with Fig. 20. ( $\times 80$ .)

Fig. 24 (Fig. 58).—Endocervix, taken fourteen days before the onset of flow. The superimposition of cells and the "honeycomb" appearance are caused by tangential section of the gland. Compare with Fig. 21. ( $\times 400$ .)



secretory phase compact and cellular. In cases of endometrial hyperplasia the papillary excrescences in the glands became exaggerated, whereas in secondary amenorrhea, of even short duration, the absence of papillations is very noticeable. Thus, Sjövall found the culmination of proliferative changes to occur not at the end of the cycle, as did Wollner, but in the middle of the secretory phase. He suggested that the marked glandular proliferation occurring in midcycle might explain the increase in cervical mucus which takes place at the time of ovulation.

This present study has demonstrated that at any given phase of the menstrual cycle, as determined by the endometrial pattern, there exists in the microscopic sections of the cervix a variety of widely different pictures. These differences are not infrequently seen on the same slide. There is no uniformity of pattern or detail. These normal variations may be caused by several factors, but it is believed that there are two major reasons. The first is the complexity of the compound racemose glands, which would present different pictures even if they possibly could be sectioned in perfectly parallel planes. The second reason is the angle at which the tissue is sectioned, resulting at times in the most bizarre patterns and the greatest irregularity in cellular detail. Thus, whether the glands are wide or narrow, short or long, straight or tortuous, regular in contour or full of excrescences will depend on which segment of the gland the microtome cuts across and at which angle to the gland it does so. The variation in the gland cells is best seen in those glands sectioned in their long axes. Here, in the same branching gland, may be seen cells which are regular in outline and moderately high columnar, cells which are arranged in a disorderly manner and compressed into very high narrow columns, cells which are cut perpendicularly to their long axes to give a so-called "honeycomb" appearance, and cells which are cut obliquely to their long axes so as to be superimposed one upon the other and give the appearance of being exceedingly tall columnar. These normal variations are present throughout the course of the menstrual cycle; they are no more prevalent in one phase than in the other. No type of variation was considered indicative of increased cellular activity or lack of activity. The only constant feature in all the endocervical specimens was the presence of secretion in the lumina of the glands. This could be seen, to a greater or less degree, in almost every gland examined under high magnification.

### Summary

1. A series of 420 biopsy specimens, 210 endometrial and 210 endocervical, was accumulated from eighty-six normal, nonlactating women during various phases of their menstrual cycles, beginning after their first postpartum menstrual period and ending six months later. These specimens were procured concomitantly.

2. Of the 210 endocervical biopsies, only 150 were considered to be histologically suitable for study. The corresponding 150 specimens of endometrium were all acceptable. Thus, a total of 300 biopsies was used for study.

3. Of the 150 specimens of endometrium, approximately half were proliferative and half were secretory, representing equally the different stages of development found during the ovulatory menstrual cycle.

4. A description of the histologic appearance of the endocervix during the menstrual cycle is given. The relationship of this appearance to the cyclic changes in the endometrium is considered.



5. A résumé of the cyclic endocervical changes reported by Wollner and Sjövall is presented.

### Conclusions

1. The human endocervix presents histologically a variety of pictures, this variation being the result of the complexity of the endocervical glands and the angle at which they are sectioned.

2. These different pictures cannot be correlated with the cyclic changes in the corresponding endometriums.

3. Specimens of endocervix presenting very similar histologic pictures are often associated with specimens of endometrium exhibiting extreme differences in their stages of development.

4. Specimens of endometrium showing identical microscopic patterns are frequently associated with specimens of endocervix which are entirely different in appearance.

5. The endocervix does not undergo cyclic changes which are demonstrable by ordinary histologic study.

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## DEXEDRINE AND WEIGHT CONTROL IN PREGNANCY\*

BERNARD I. COOPERSMITH, M.D., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, Northwestern University Medical School and Michael Reese Hospital)*

THE control of weight during pregnancy is one of the important aspects of prenatal care. Obesity in the nonpregnant patient is a serious threat to health since it predisposes to diabetes, cardiovascular-renal diseases, and definitely shortens the life span of the individual.<sup>1</sup> The addition of pregnancy may increase the obesity, which, it is claimed, may predispose the patient to dystocia, prolonged labor, and toxemia.

Many methods for weight reduction have been used, with varying results. The oldest and simplest is diet. Also commonly used are catharsis and/or diuresis, but these have obvious objections. Atropine sulfate had its advocates who claimed that by drying mouth secretions, it reduces the appetite. Its effect, however, is not always predictable, and its use is not free from danger. Various emetics and nausea-producing drugs have been tried and discarded. The introduction of dinitrophenol was heralded as a panacea for obesity, but, with its widespread use, its toxic effects were soon discovered, and the drug was condemned.

The mention of desiccated thyroid for weight reduction arouses a controversial storm. Its widespread use only serves to emphasize the warning by the Council on Pharmacy of the American Medical Association against the "fallacy and dangers of overstimulating the body with thyroid."<sup>2</sup> It is indicated only in hypothyroid states, and its indiscriminate use should be deprecated.<sup>3</sup> Thyroid increases the appetite, does not always reduce weight, and is toxic in many cases.

Medical consensus holds that most obesity is psychogenic in origin. The old idea of "glandular imbalance" was exploded by Newburgh<sup>4</sup> and others<sup>1</sup> who showed that obesity is simply due to excess caloric intake in relation to caloric expenditure for a particular individual. Psychic factors which may result in constant overeating are variable and include emotional tension, fear, anxiety, frustration, a feeling of insecurity, monotony, and subconscious factors due to infantile personality, such as the urge for oral gratification. Pregnancy, with its multiplicity of new and varied experiences, usually intensifies these emotions.

Therefore, any drug which could decrease appetite, stimulate the patient mentally and physically, reduce boredom, raise "morale" and be relatively non-toxic would be the ideal choice for weight control. Dexedrine sulfate fits this picture fairly well.† Dexedrine sulfate is dextrorotatory amphetamine sulfate,

\*Presented at a meeting of the Chicago Gynecological Society, Oct. 15, 1948.

†Dexedrine is the proprietary name for dextrorotatory amphetamine manufactured by Smith, Kline and French Laboratories. The name Dexedrine will be used in this report for the sake of brevity.

the racemic mixture being the more commonly known Benzedrine sulfate. Oddly enough, the effect of Benzedrine on appetite was first noted as a side reaction when the drug was used in psychiatry for the relief of depressive states. Numerous reports on its use in the treatment of obesity have since appeared in the literature.<sup>5, 6, 7, 8</sup> Dexedrine has a similar effect on appetite and was considered more desirable than the racemic compound for trial during the prenatal period because it produces fewer side reactions.

Many theories have been proposed to explain the mode of action of Dexedrine in weight control. They include a diuretic action on the kidneys, an increase in the basal metabolic rate and energy utilization, a direct action on the gastrointestinal tract to reduce hunger, and a direct action on the central nervous system to reduce appetite and stimulate activity. However, Harris, Ivy, and Searle<sup>9</sup> and others have shown that Dexedrine has virtually no effect on the kidneys, basal metabolic rate, or gastrointestinal tract. It acts on the central nervous system causing anorexia, with resultant reduction in food intake and also improves the general mood of the patient.

Dexedrine has an extremely low toxicity, and its therapeutic margin is so wide that it can be given safely in man even in doses many times the therapeutic amount.

#### Procedure and Methods

The present series covers the years 1945, 1946, and 1947, during which 100 pregnant patients were given varying amounts of Dexedrine sulfate in an attempt to control excessive weight gain. These were all carefully supervised private patients, part of a total of 563 private patients delivered during the period of study. There were fifty-two primiparas and forty-eight multiparas. Of the multiparas, thirty-four had previously been delivered by the author without the use of Dexedrine. Because of excess weight gain in their last pregnancies, the drug was prescribed early in the present pregnancy. This group shows the greatest differential as to weight control.

The drug was prescribed for the balance of the multiparas and all of the primiparas only after usual methods, such as instructions to limit salt and fluid intake, 1,200 calorie diet, and repeated warnings relative to the dangers of obesity failed to produce the desired results.

Twenty-two patients of the total 100 took desiccated thyroid in dosages of from  $\frac{1}{2}$  to  $1\frac{1}{2}$  grains daily, because of low basal metabolic rates, but this did not control their weight satisfactorily, and Dexedrine was also prescribed.

The average dose of Dexedrine sulfate was a 5 mg. tablet taken at 10:00 A.M. and repeated at 3:00 P.M. Some patients subsequently had to double the dose, but no patient received more than a total of 20 mg. daily. The time interval for giving the drug was chosen to gain maximum appetite abatement for lunch and supper, the largest meals, without producing insomnia caused by taking the drug too late in the day. This proved a satisfactory arrangement. All patients were given a diet complete in nutritional requirements except for the total calories which were limited to 1,000 to 1,200. In addition, a capsule containing multivitamins, calcium, and iron was prescribed to supplement the diet and prevent avitaminosis and anemia.

The length of time the drug was taken varied from one to six months. The majority of those patients who did not receive the drug prophylactically began taking Dexedrine at the end of the second or beginning of the third trimester when it became apparent that they had gained weight excessively in spite of repeated warnings and the usual measures previously mentioned.

After a period of weight loss, the drug was discontinued and in many instances, no further treatment was necessary because of the development of new eating habits. It was noted that the use of Dexedrine for a period of four to eight weeks produced a tolerance to the drug in some patients. After a rest period of one to two weeks, this tolerance disappeared and the drug again became effective in reducing appetite.

For a control series, 200 consecutive obstetrical patients were taken from the years before Dexedrine was used and their total weight gain averaged. Sixty-nine of these patients were on 1,200 calorie diets, and thirty-nine took varying amounts of thyroid.

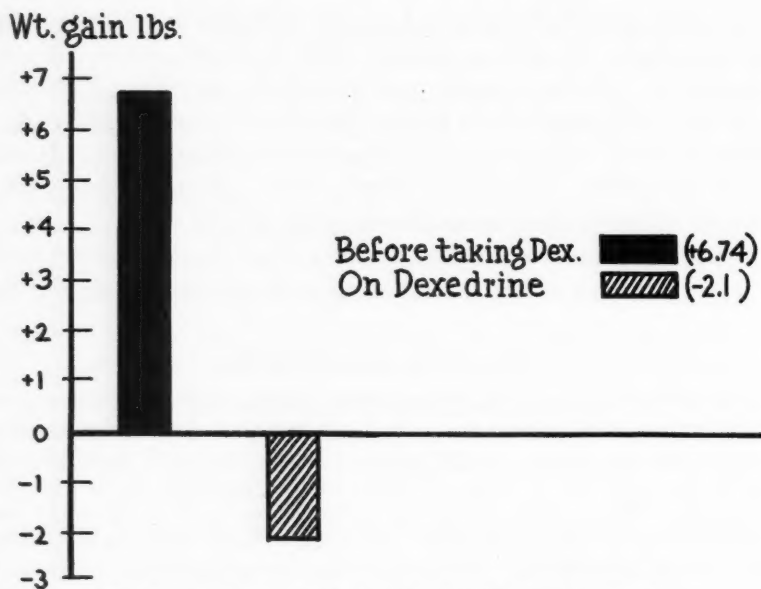


Fig. 1.—Average weight gain during four-week period.

When this series was begun, it was not the purpose of the treatment to reduce obese patients during pregnancy, but rather to control their weight gain. Toward the end of the series, it became apparent that obese patients could safely reduce during pregnancy with the use of Dexedrine, either by starting the drug prophylactically early in pregnancy or using larger and more frequent doses. Finch,<sup>10</sup> using larger doses of Dexedrine, reported an interesting series in which the weight of seventy obese, pregnant patients was controlled with Dexedrine. Eight weighed less at delivery than at the onset of pregnancy. He concluded that Dexedrine is a valuable and safe drug to use in preventing excessive weight gain in obstetrics.

### Results

Twelve of the 100 patients who received Dexedrine began its use at the first prenatal visit. In the remainder of the patients, a comparison of weight gain during a four-week period prior to taking Dexedrine, but on a 1,200 calorie diet, showed an average gain of 6.74 pounds for each patient, the smallest being 4 pounds and the largest, 12 pounds. These patients, taking Dexedrine during the following four-week period, showed the following: fourteen patients gained one to two pounds; twenty-one remained the same; and fifty-three lost from one to nine pounds. There was an average net loss of 2.1 pounds per patient (Fig. 1).



The total weight change for the entire pregnancy of the 100 patients taking Dexedrine varied from a gain of 23.5 pounds to a loss of 5 pounds, an average gain of 17.7 pounds per patient, as compared to 26.42 pounds per patient for

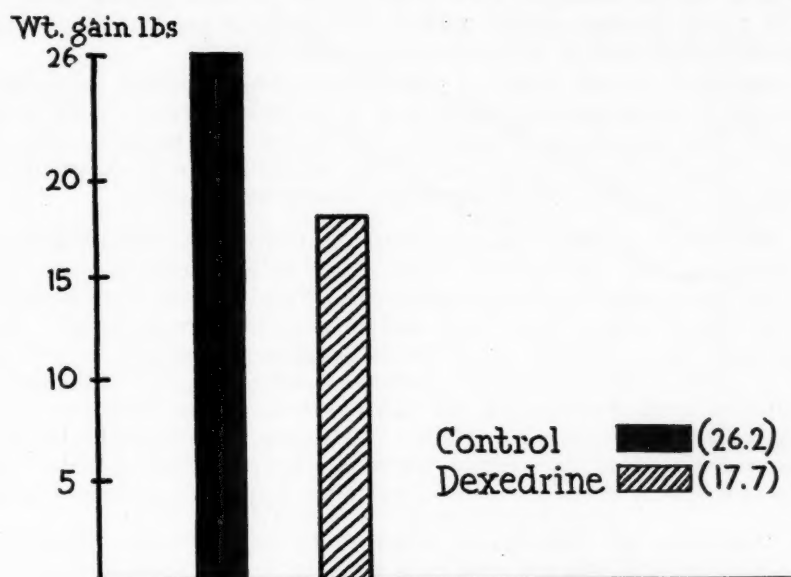


Fig. 2.—Average total weight gain during pregnancy.

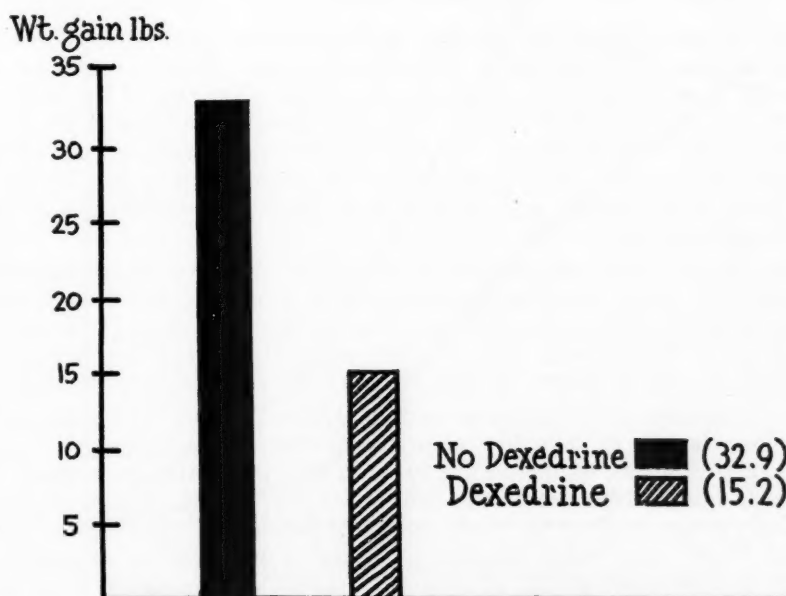


Fig. 3.—Average weight gain of thirty-four multiparas during two successive pregnancies.

the control series (Fig. 2). Thirty-four multiparas in this series had been under the author's care for their previous pregnancies, during which they gained from 25 to 43 pounds total, an average of 32.9 pounds per patient. This occurred in

spite of thyroid and careful instructions as to restricted diets. Many in this group began taking Dexedrine early in their present pregnancies, twelve at the first prenatal visit. Nine weighed the same or less at delivery than when they started. The weight change varied from a gain of 22.5 pounds, to a loss of 5 pounds, or a net average weight gain of 15.2 pounds per patient, compared to 32.9 pounds average gain in previous pregnancies (Fig. 3).

As previously stated, many of the patients began taking Dexedrine about the sixth month of pregnancy when their total weight gain was as much as or in excess of that considered normal for the entire nine months. Fig. 5 shows the normal weight curve compared to the weight curve of a treated patient illustrating the controlling effect Dexedrine has on weight gain.

One patient was an obese primipara with an essential hypertension known to exist prior to pregnancy. She was referred to the author by her family physician because of steadily rising blood pressure without albuminuria. When first seen at twenty-four weeks' gestation, her blood pressure was 172/92 and no albuminuria was present. Her weight was 214 pounds, compared to 182 pounds before pregnancy, a gain of 32 pounds. There was no gross edema. She was given a salt-free 1,000 calorie diet with limited fluids, phenobarbital,  $\frac{1}{4}$  grain three times a day, and Dexedrine. Four weeks later she had lost 9 pounds and her blood pressure was 168/92. The regime was continued with omission of phenobarbital and at term she weighed 188 pounds and her blood pressure was 154/88, a reduction in weight of 26 pounds with a concomitant drop in blood pressure (Fig. 4).

This illustrates an observation reported by others,<sup>10</sup> that essential hypertension associated with obesity responds to weight reduction during pregnancy as it does in the nonpregnant state, and that Dexedrine is not contraindicated in hypertension.

### Discussion

About 30 per cent of the patients said that they felt better, less tired, and were able to carry on their duties with greater ease. When Dexedrine was prescribed early in pregnancy, many of the annoying symptoms of the first trimester such as nausea and physical inertia were alleviated in varying degree, probably due to its antidepressant action. In some patients the results were remarkable.

Almost all of them were grateful for the aid the drug gave them in controlling their food intake, and were happy when contemplating the cosmetic result of weight control.

About 20 per cent complained of a mild irritability which usually disappeared in a few days, even though the drug was continued. It was noted that irritability seemed greatest in those patients taking both thyroid and Dexedrine, so that recently thyroid was discontinued when Dexedrine was begun. Eleven patients complained of insomnia which was easily controlled with mild sedation.

The commonly cited dangers and contraindications to amphetamine are hypertension, danger of habituation in susceptible individuals, and excess nervousness. In this series, as in most reports in the literature, no increase in blood pressure was noted from use of the drug, and, conversely, in hypertension associated with obesity, a drop in blood pressure was noted with weight reduction. Freed and Finch also report similar findings. There was no evidence of habit formation in this small group of patients. However, we agree with the literature that amphetamine should not be given to highly nervous individuals who exhibit a hypersensitivity to the drug.

Many physicians are able to control their patients' weight gain by enlisting their "cooperation," but too often this consists of bullying and threatening them. It is an interesting fact, reported to me by many of these patients, that after such an office visit they will go home and indulge in excessive carbohydrate

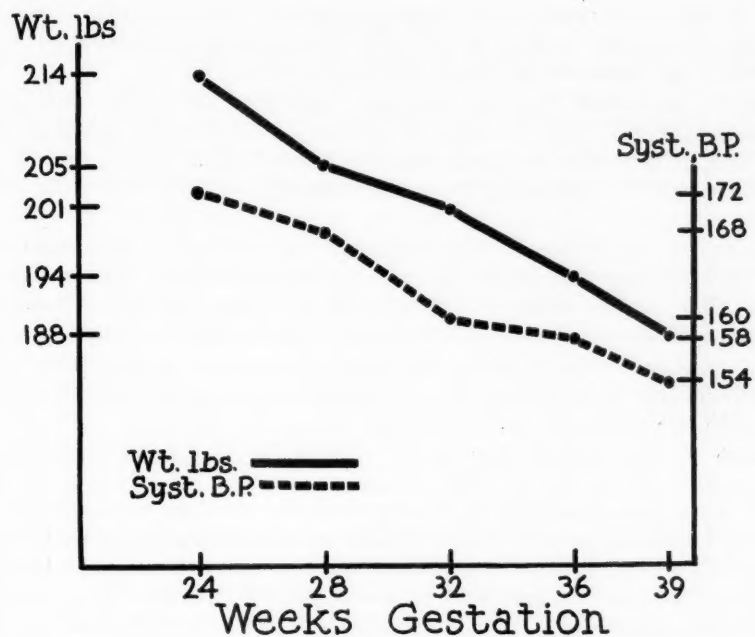


Fig. 4.—Essential hypertension in pregnancy responding to weight reduction with Dexedrine.

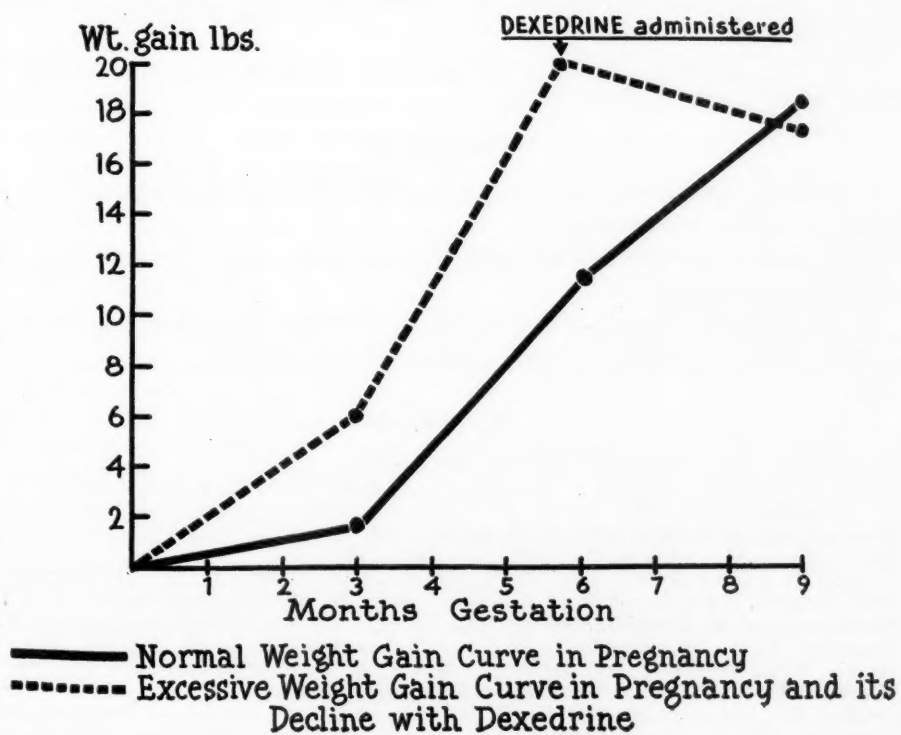


Fig. 5.

intake as a result of their own frustration and the animosity aroused by the obstetrician. One may further elicit, with sympathetic questioning, that episodes of excessive weight gain often follow domestic crises.

Luikart<sup>11</sup> reported that no toxemia occurred in 1,000 normal obstetric patients whose weight he was able to control. These were selected cases, however, as those who would not cooperate were omitted from the series. It is just these uncooperative patients who need Dexedrine to aid their attempts at diet control.

In spite of evidence to the contrary,<sup>13</sup> a few men feel that controlling weight gain in the mothers will control size of the babies. Luikart believes this and states that in his series, "There were no large babies. One baby whose parents were both over six feet tall weighed nine pounds two ounces."

In the present series, the babies were of average weight. Six infants, all boys, weighed over 9 pounds. Finch reports that in his group, "The babies were all well nourished and of normal size."

Toxemia merits special discussion. Dieckman<sup>12</sup> states, "Extensive experience has confirmed the belief that excessive and too rapid gains in weight are associated with pre-eclampsia and eclampsia in a high percentage of cases." In his book, however, he adds that Siddall and Mack found no relation between the amount of gain and severity of toxemia and that they found no toxemia in 45 per cent of the normal patients who had gained excessively. Luikart's series of 1,000 weight-controlled normal pregnancies without toxemia has been mentioned.

In the present series, no case of pre-eclamptic toxemia occurred in the treated patients. Four of the multiparas who had gained excessively in their previous pregnancies and developed mild-to-moderate pre-eclamptic toxemia had none in the present series.

It is felt, however, that this series is too small to draw any conclusion as to the relation of obesity to toxemia.

### Conclusions

1. Psychic factors are paramount in producing obesity and these are often multiplied during pregnancy.
2. Dexedrine sulfate is a safe and effective drug to use in controlling weight gain during pregnancy.
3. Dexedrine in dosages effective for the control of appetite has no deleterious effect on blood pressure, and may be used in hypertension.

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### Discussion

DR. EDWIN J. DeCOSTA.—What constitutes excessive weight gain during pregnancy? A total gain of some 17 pounds will account for the weight of the fetus, placenta, liquor, hypertrophy of the breasts, and increased blood volume. Is weight beyond that excessive? Some authorities maintain that this is so.

What is the objection to so-called excessive weight gain? If the patient is near optimum weight for her age and height at the time of conception, moderate weight gain per se does not appear to lead to dire consequences. When I refer to moderate weight gain, I mean 20 to 30 pounds. Excessive and rapid weight gain may be associated with toxemia but this does not mean that the gain is responsible for the toxemia. Toxemia is often associated with marked fluid retention and consequent weight gain, but toxemia also occurs without weight gain. The most fulminating, severe pre-eclamptic toxemia I have cared for in the past several years occurred in a patient whose full-term weight was only 3 pounds greater than her conception weight. This patient had taken Dexedrine. Her nonpregnant weight was 178 pounds and weight control was primarily for esthetic reasons.

Obese patients, that is, those who are obese prior to conception, particularly those who weigh over 200 pounds, present a variety of problems. Certainly obesity predisposes to heart disease, hypertension, diabetes, poor posture, and orthopedic complaints. During pregnancy these conditions are likely to become exaggerated. In addition, toxemia, postpartum hemorrhage, prolonged labors, malpositions, and large babies are encountered more frequently, and both maternal and fetal death rates are higher than average. However, in Dr. Coopersmith's presentation, he is not specifically concerned with the obese patient. He is only concerned with excessive weight gain as observed during the course of recent or previous pregnancies. This gain I assume is due to fat deposit and not to water retention, as caloric control should not affect electrolytic balance. He has demonstrated his ability to control weight gain by the use of Dexedrine where suggestion and counsel have failed. However, since simple obesity is believed to be psychogenic, induced anorexia and limitation of diet are solely symptomatic therapy and do not reach the underlying cause.

In addition, there is the danger that dietary restriction may lead to inadequate diet, which in turn may result in impaired lactation and bodily function. The generally accepted daily protein requirement during the last trimester of pregnancy is 1.5 Gm. per kilogram of body weight. This amounts to 85 to 110 Gm. of protein. The carbohydrate and fat needs have never been accurately established but accepted amounts generally are carbohydrate, 250 to 400 Gm., fat 70 to 140 Gm. This will provide a diet varying from 2,000 to 3,400 calories. If the patient is to cease gaining or actually lose weight it is obvious that the caloric intake must be something less. Since protein is essential and a diet to be palatable must contain at least 50 Gm. of fat and 150 Gm. of carbohydrate, it is difficult to provide a satisfactory diet of less than 1,400 calories. Dexedrine, by spoiling the appetite, helps the patient to stay on a low caloric diet, but I wonder if we might not err seriously in leaving dietary decisions to these patients. I question whether they would take the kinds of foods they need.

The vitamin and mineral content (calcium, phosphorus, and iron) must be optimum. Mineral and vitamin needs may be at least partially met by supplemental feeding. Recently there has been some indication that water retention may be associated with vitamin deficiency as well as excessive sodium intake. The relationship is involved and includes consideration of progesterone metabolism and liver function in the process of sodium ion mobilization and capillary permeability.

The body's capacity for self-protection is miraculous but when excessive demands are made and protein, mineral, and vitamin needs are barely met, recuperative power can be seriously affected. I have seen poor healing of both abdominal wall and uterus following cesarean section in a patient whose weight was rigidly controlled. Ten days after cesarean section, she had to have a hysterectomy as a lifesaving measure in order to stop

acute uterine hemorrhage. The edematous, boiled appearance of the tissue suggested the urgent need of proteins and vitamins, and following their administration her convalescence was rapid and uneventful.

Rigid weight control may keep the patient in good "form." Simple obesity does little harm, but lack of attention to dietary requirements can cause serious disturbances in the mother, the newborn, and the growing child.

DR. M. EDWARD DAVIS.—The control of weight gain during pregnancy is an important phase of good prenatal care. The ideal weight increment for the normal woman has not been ascertained. At the Chicago Lying-in Hospital we try to limit the total gain to 16 to 18 pounds. We make allowance for the woman who starts her gestation weighing less than her optimum amount and allow a greater increase during pregnancy. Likewise, we decrease the weight gain permitted the woman who is overweight. It is important that weight increase be distributed in such a way that about two-thirds the gain occurs during the last trimester of pregnancy, the period during which the fetus grows most rapidly.

Excessive weight gain during pregnancy is a hazard to the mother and her baby. In our clinic Dieckmann has shown that women who gain more than 30 pounds have twice the incidence of toxemias of pregnancy than women who gain less than 20 pounds. Furthermore, the obese woman is more likely to have complicated deliveries resulting in an increased fetal mortality.

It has been our practice to limit weight gain by dietary management alone. Frequent visits to the nutritionist are not always followed by ideal weight control. Often the obstetrician has to read the riot act to the patient in order to accomplish the desired results.

If the use of Dexedrine will aid in the intelligent management of the prenatal patient without harmful results it will be a useful drug. However, larger and more carefully controlled groups of patients will have to be studied to determine its value and its freedom from undesirable complications.

DR. COOPERSMITH (Closing).—Dr. De Costa began as I hoped he would, by saying that obesity is shown to be of importance in obstetrics. I agree with him. Then he began to differentiate between weight gain and obesity which, of course, is important. On the other hand, where does weight gain stop and obesity begin? One shades into the other. In taking care of paras iv and v who weigh about 200 pounds or more, we very often get a history that they gained 30 or 40 pounds with their first pregnancy and they retained 10 or 15 pounds of that, and then they increase in weight with each pregnancy until they come in with their fifth and are obese. If we could get them in their second or third pregnancy, we might prevent the development of obesity.

The role of the physician in weight control has been pointed out. It is that of a father confessor. Those patients who put on excess weight have problems, either about their mothers-in-law, finding an apartment, or with their husbands, and they eat constantly as an outlet. If the physician could spend time with them and talk over their problems, I have an idea we would need less Dexedrine. I think Dexedrine is helpful in controlling appetite and in giving "mental poise." I have had patients come in who had gained excessively in previous pregnancies taken care of by someone else. After they had gained 20 or 25 pounds, they were told, "If you gain more weight you will have to go to another obstetrician." These patients need help, and bullying and threatening them is not the correct approach.

## SURGICAL TREATMENT OF STERILITY\*

ROBERT N. RUTHERFORD, M.D., HOWARD M. LAMBORN, M.D., AND  
A. LAWRENCE BANKS, M.D., SEATTLE, WASH.

WITH newer methods of diagnosis, sterility studies have assumed a more exact nature. With increased hormone knowledge and potent inexpensive preparations, hormone reinforcement of lagging reproductive effort has become possible and requires no apology. With an adequate male partner, and with an adequate pattern of ovulation, many female patients present themselves still as difficult cases. These constitute by far the most common problems presented in sterility where the female factor alone is at fault. Pre-eminently that fault is tubal occlusion.

Correction of tubal occlusion cannot be handled by hormone attack. It yields either to pressure methods from below, or must be attacked surgically from above. With the use of pressure methods involving either gases or radiopaque media, pressures up to 200 mm. of mercury can be employed safely at monthly intervals for an indefinite period of time. If these procedures are planned for shortly before ovulation is expected, a very satisfactory "take" rate has been reported from many workers in this field. However, those patients who fail to achieve tubal patency by these methods, when they are tried conscientiously and skillfully over an adequate period of time, are left as a hopeless residual for whom surgery seems the only relief.

### Plan of Study

Some six years ago, a routine treatment was established for both primary and secondary sterility patients. This pattern follows closely the sterility work-up regarded as essential and minimal by the American Society for the Study of Sterility. If the male partner is potent, and if the patient is ovulating habitually, with tubal occlusion as the only obvious problem in the case, then she is committed to monthly efforts to relieve this obstruction. The Rubin's test is used as a screening test only and, if on two successive months no gas passes, the patient is next assigned to Lipiodol tubal insufflations. Great care is taken in timing these patients' procedures. Rather than relying upon the basal temperature curve alone, the writer prefers to calculate a fertile phase for each patient, embracing the period of from eighteen through ten days before flow is expected. Ovulation usually comes in the mid-zone of this phase, but variation is given for the few days of sperm life in the vagina before ovulation and the possible life span of the ovum after its release. In other words, the effort is to replenish the sperm supply in the vagina every two to three days during this fertile phase. This may be of more value than withholding exposure until the basal temperature curve shifts upward. Work in artificial insemination techniques would tend to substantiate this impression.

The patient must have a minimum of three Lipiodol uterotubograms *without* progress in tubal dilatation before surgery is considered. The large majority

\*Presented at the Second Annual Conference, Western Section, American Society for the Study of Sterility, February, 1948, San Francisco, Calif.

of the patients in this study had four to six before nonsurgical methods were abandoned. All patients had partners whose sperm studies were at or above the recognized minimum requirements. They were put empirically on daily one grain dosages of desiccated thyroid extract, checked by a metabolism test. There were routinely given 0.5 mg. dosages orally of stilbestrol from four days following the end of one menstrual flow to within seven days of expected flow. This was an effort to increase cervical mucus permeability. As well, the patients were instructed to douche shortly before intercourse with Nutri-Sal, a "sperm nutrient" douche. On the advice of several urologists working in the study, the husbands were on from one-half to one grain thyroid daily dosages as well, empirically, despite metabolism readings or total sperm counts. Since the beginning of the study, three husbands have been replaced by donors. There have been two successes.

### Operative Techniques

Actually, a combination of techniques often appeared in the same patient, posing in this fashion some question in classification. For example, one might circumcize the tube on one side, whereas the other tube would require circumcision plus reimplantation. Or, a myomectomy might have to be combined with a resection of endometrial implants, plus fulguration of other implants. Despite these difficulties, the cases are classified by the greatest problem presented in disorder of tubal function, and combinations of techniques are minimized.

1. *Salpingolysis* was required in seven cases, where tubal occlusion had been uncorrectable from below, but which was corrected once the tube or tubes were released from extratubal obstructions. This hampering of tubal function is akin to intestinal obstruction on a like basis, and leaves the tubal lumen undamaged. Care was taken to peritonealize all raw areas meticulously, to be certain that the tubal fimbria maintained their close proximity to the ovaries, and in only two cases was suspension of the tube deemed necessary to prevent readherence in the posterior cul-de-sac. Results in this small group should be deservedly good, for these are indirectly "obstructed tubes."

2. *Salpingostomy* was required in sixteen cases of the group. Two general techniques were employed, either the cuff method of Sovak where the occluded fimbria was removed completely, and then a symmetrical cuff of mucosa was inverted back over the remaining tube, or else the fimbria, if not too badly damaged, was opened as by a dorsal slit on the antimesenteric border (to avoid vascularity and impairment of blood supply) and then the two triangular-shaped flaps were sutured back along the tube. The judgment of the operator dictates the choice.

3. *Probing* open of isthmic obstruction followed by irrigation of the tube with saline using a Chetwood syringe was required in eleven cases. This type of obstruction is suggested by a narrowing of the isthmic portion of the tube and by the finding of small nodules on the serosal surface of the tube, the so-called "chronic isthmic salpingitis" spoken of by the pathologists. Damage to the tubal mucosa is high here, but apparently the results are better if one probes and does not resect this area to reimplant the short distal segment left. This type of occlusion can be relieved very well by insufflation from below at a later date, once the original fibrous closure is relieved by dilatation.

4. *Resection* of the proximal portion of the tube and reimplantation of the distal portion into the uterine cornu were performed in six cases with success in only two. A very real addition to technique in these cases is to open the uterine cavity by a vertical incision into the fundus. The bivalved uterus then can be inspected for the occluded uterotubal junction and then probing can be done from the uterine and not the tubal side. This is of real advantage, for many false passages are made by forcible probing or irrigation of the tube in this



region where it narrows normally to an extremely small calibre, plus an increased narrowing from the valve found at this end of the tube. If the uterus is opened and the probing is done in the fashion suggested, results in probing open this obstruction have been better. If it cannot be probed open, then the cornual resection of the occluded portion can be done under direct vision and the drawing of the tube through the channel in the uterine muscle and its fixation performed with dispatch. This is of real value. The proximal end of the resected tube is split and each leaf sutured apart. Both successes were delivered by cesarean section because of the possible danger of rupture of any of the three scars. Three cases where vestigial tubal structures were shaped about a ureteral catheter or a tantalum guide were unsuccessful.

5. *Implantation* of the ovary was performed in three cases. There were no successes. Two of these patients had had previous salpingectomies and one had had a tubal ligation for purposes of sterilization. No justification can be given for these cases except that the patient wished surgery despite surgical risk and a virtually hopeless outlook for success. Two of these have subsequently adopted babies. A slice of the uterus was removed from each cornu to expose the endometrium. The Estes' operation was followed except that the ovary was not resected to implant a raw surface into the uterine lumen. Since the ovarian cortex is the site where follicles are found, it seemed unwise to remove this area and to present scarred stroma to the uterine cavity. The ovary was sutured in place. Only one ovary was so treated, the other ovary being left untouched. Cystic degeneration is always a danger in ovaries which are left in a pelvis which has been operated upon. This implantation of the ovary probably does not add to this danger greatly. Since only one ovary was implanted in these three cases, the writer now is struck by his illogical optimism which would hope that the implanted ovary would be the one to ovulate preponderantly.

#### Aftercare

Nothing new of significance has been added by the operative techniques outlined so far. These are standard procedures in the armamentarium of every operating gynecologist. It would seem, then, that better results would come only from the aftercare and from this alone. If the tubal physiology is so damaged that it no longer is a conducting mechanism but is merely an inert hollow channel forced open periodically by pressure from below, no amount of aftercare will restore the damaged part. However, here is where optimism focuses attention.

The patients were put on both sulfonamide therapy and penicillin therapy twenty-four hours before surgery, and this was continued for five to seven days after surgery. Forty-eight to seventy-two hours after surgery, the patient was insufflated with pressures up to 200 mm. of mercury. Not infrequently passage of air was noted immediately. In the majority of cases, 77.5 per cent to be exact, this first air insufflation was unsuccessful, due probably to edema of the tube, plus a certain amount of bleeding. Often while one is still operating on the tube, it will become edematous and increase enormously in size. The insufflations are done every three days thereafter until tubal patency is established and maintained for three tests. These tests are interrupted only for menstrual flow. Unfortunately, since the uterus decompresses itself of pressured gas upon the opening of only one tube, often only one tube can be kept open. Following establishment of patency on three successive tests—occasionally false negative results are given during the "spastic phase" of the tube—the patient then has a Lipiodol uterotubogram to demonstrate tubal silhouette and patency. Early in the study, tubal peristalsis was followed using the fluoroscope. This is a valuable procedure. Then, once patency is proved by uterotubogram, Lipiodol studies are done at two- to three-month intervals until pregnancy ensues. Of the group of patients operated upon who did not become pregnant, some twenty-two cases,

three have occluded again and have become refractory to further treatment. In four others, efforts at insufflation had to be abandoned because of either flare-up of the previous (or a new) pelvic infection or because of a chemical peritonitis from iodized oil. These patients responded to chemotherapy but further efforts lie along adoption lines. No deaths occurred.

### Case Histories

It was thought advisable to present a success and a failure in each group with preoperative and postoperative uterotubograms in an effort to analyze the factors in selection of cases for surgery, operative treatment, and aftercare, with causes for failure.

#### *Perisalpingitis.*—

Mrs. G. H., is a 25-year-old housewife, never pregnant, who presented herself as a primary sterility patient of four years' duration. Work-up of the couple was normal except for a 10 cm. left ovarian cyst. Two Rubin's tests were done, but before Lipiodol studies could be started, she had to be operated upon for an acute abdominal emergency because of twisting of the cyst. At operation, a ruptured necrotic dermoid cyst was found, requiring a left oophorectomy. Both tubes were edematous, twice normal size, and bound down to the posterior broad ligament leaves. Other viscera were negative although the patient had had a previous appendectomy as an interval procedure for chronic abdominal pain. Once the fimbriae were mobilized as well as the rest of the tubes, irrigation with saline was performed without difficulty. The patient has since had two pregnancies.

#### *Fimbrial Occlusion.*—

CASE 1.—*Success.* Mrs. M. B. is a 33-year-old housewife, with a sixteen-year story of known gonorrhea. She had had in 1940 a right salpingectomy for a ruptured ectopic pregnancy, and oil later "showed a tumor of the end of the remaining tube." She presented herself first in 1945 because of secondary sterility and chronic left lower quadrant pain. Work-up of the couple was normal with a completely negative pelvis. Four uterotubograms (Fig. 1) are presented demonstrating progressive dilatation of the left tube from occlusion in the midportion on to complete distention of the tube without passage through the fimbria. The last picture of the series shows a left hydrosalpinx without further success in dilatation. Much larger amounts of Lipiodol often will simply sacculate in such a hydrosalpinx without pressure building up to open the fimbria. Interestingly enough, the resected right tube has opened for the proximal half.

At surgery, the right tube was half present. This was opened, circumcised by Sovak's method, and passed saline and probe easily. The left hydro-salpinx was opened, the circumcision was performed by the dorsal slit method. The rugae looked edematous but normal in pattern with minimal scarring. Both ovaries were mobilized from old adhesions and sutured to the round ligaments. Air passed two days later at 110 mm. of mercury. Heavy chemotherapy was continued for two weeks.

The next three x-ray pictures (Fig. 2) demonstrate the postoperative result taken at three-month intervals following surgery. The patient became pregnant two months after the last uterotubogram, eleven months after surgery.

CASE 2.—*Failure.* Mrs. A. P. is a 32-year-old housewife with 12 years' primary sterility. Work-up of the couple was negative except for a uterus about twice normal size with multiple small subserous fibroids. Fig. 3 demonstrates the failure of oil to go beyond the isthmus covering five uterotubograms at monthly intervals. At operation, multiple myomectomy was done, with bilateral circumcision of tubes for hydrosalpinx which destroyed the distal half of the tubal mucosal pattern. Resection was performed and a new fimbria created by the dorsal slit method bilaterally. The x-rays in Fig. 4 demonstrate reconstruction of the tubes with eventual passage of oil nine months after surgery. Air passed at pressures of 180 mm. of mercury three days following surgery, and at three-day intervals. The tube has been kept open for two years following surgery with no result.

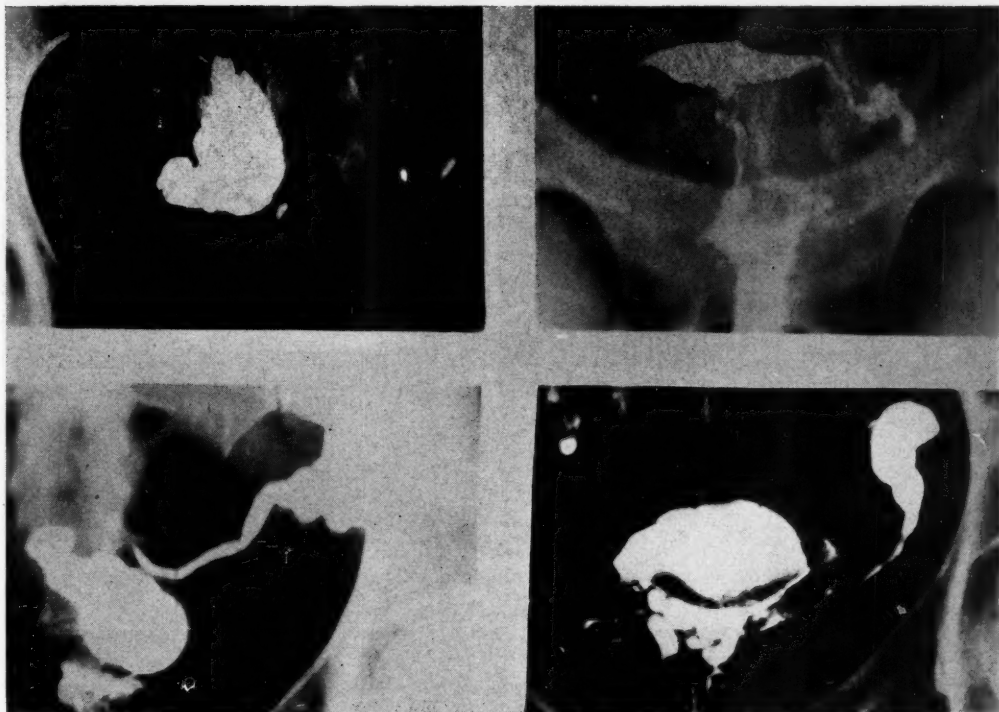


Fig. 1.—Progressive dilatation of left tube from occlusion in midportion on to complete distention of tube producing left hydrosalpinx without further success in dilatation. Right tube (previously resected for ectopic pregnancy) has been opened for first half.

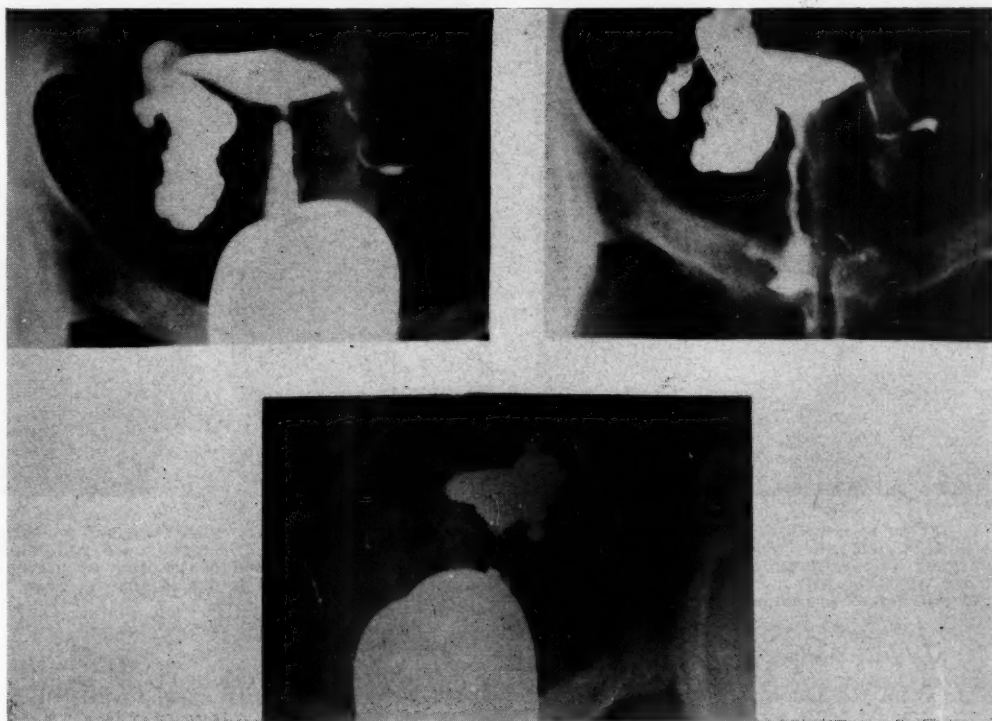


Fig. 2.—Next three x-ray pictures demonstrate postoperative result taken at three-month intervals following surgery. Patient became pregnant two months after last uterotubogram, eleven months after surgery.



The patient was given an adoptive child in the interim and is continuing her effort. A more extensive hydrosalpinx in Case 1 did not result in failure because the tubal mucosa was much less damaged than in either of these tubes, although the over-all dilatation in Case 1 was greater.



Fig. 3.—Failure to go beyond the isthmic portion over five uterotubograms.

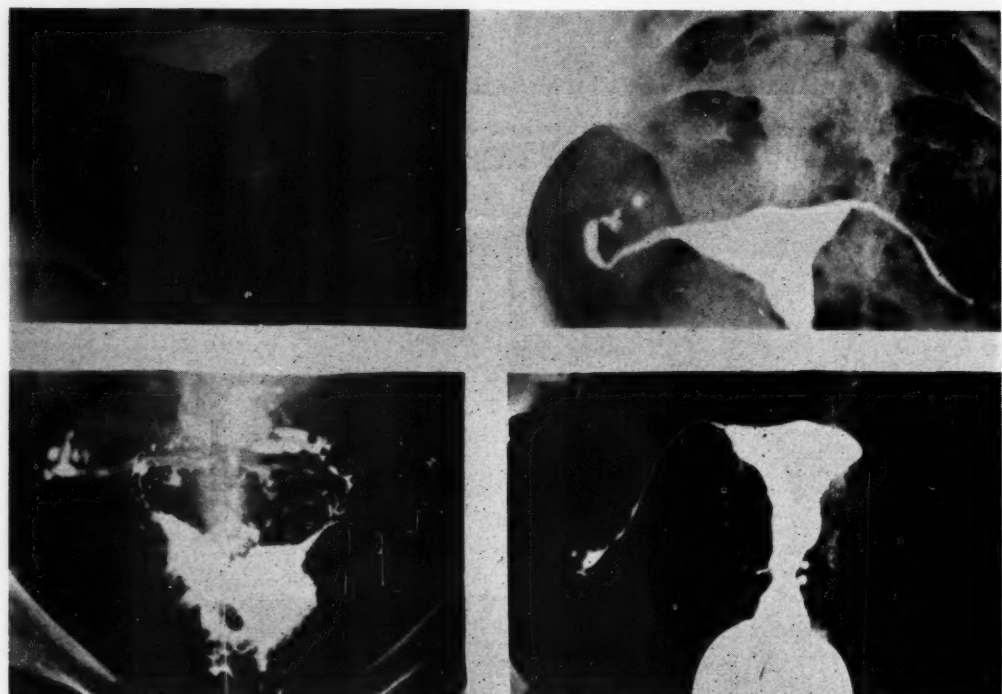


Fig. 4.—Postoperative result showing reconstruction of both tubes, with eventual passage of oil on left nine months after surgery. Tube has been kept open for two years following surgery with no pregnancy ensuing. Hydrosalpinx found at surgery, and destruction of normal tubal architecture and physiology probably cause. A more extensive hydrosalpinx in Case 1 did not defeat pregnancy.

#### *Isthmic Occlusion.—*

**CASE 1.—Success.** Mrs. E. H. is a 36-year-old housewife, married eight years, with an uncured spontaneous abortion in 1939. Check-up on the couple was normal but for tubal occlusion. The x-rays in Fig. 5 show the first and last uterotubograms in a series of six



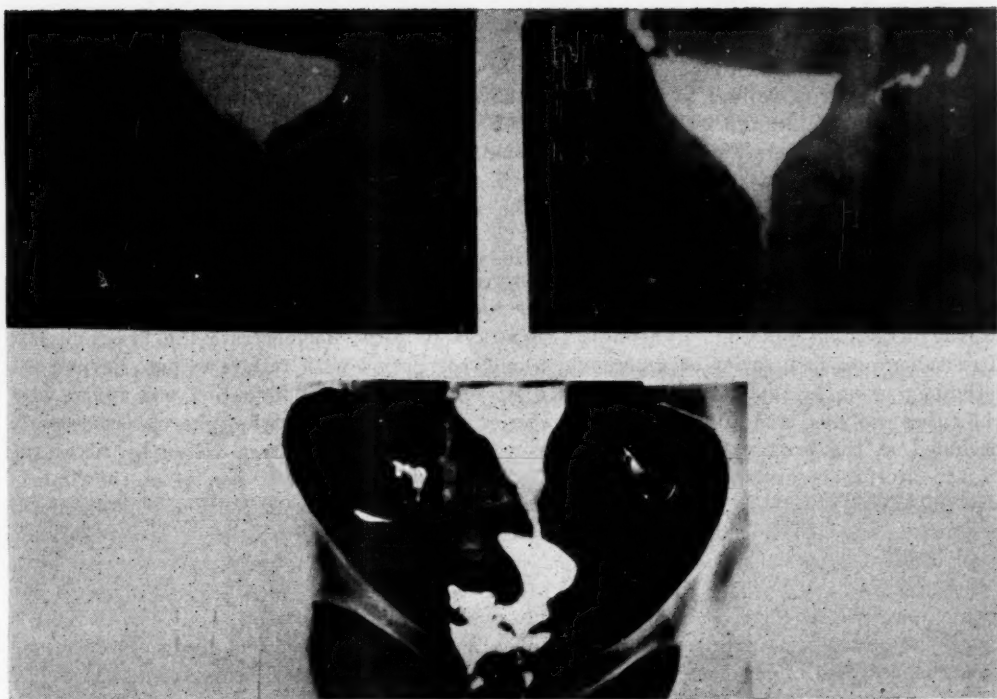


Fig. 5.—First and last uterotubogram in a series of six over one year with failure to pass beyond the isthmus portion in any. Postoperative result demonstrating tubal patency bilaterally one month after surgery. Pregnancy ensued with the accompanying fertile period. Patency achieved by probe and irrigation.

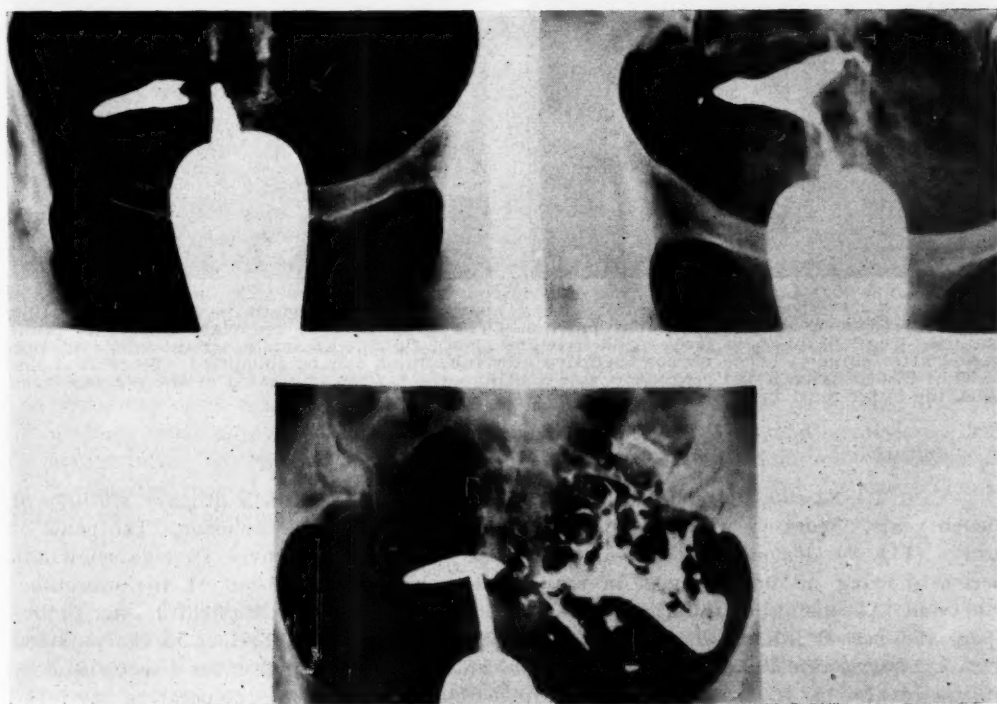


Fig. 6.—First and last uterotubogram in series of seven over one year with failure to pass beyond isthmus portion in any.

Postoperative result demonstrating passage freely on right, the inner third of which was probed open and irrigated, but which was reimplanted because interstitial portion was hopelessly occluded. Left tube was probed open after fimbria was circumcised. This failed to stay open. Failure to achieve pregnancy probably due to disorder of physiology subsequent to implantation of tube.

over one year with failure to pass beyond the isthmic portion in any. At operation, both tubes were closed in the isthmic portion, but the fimbriae were patent. Both opened on probing and the interstitial portion was normal. Air passed at 180 mm. of mercury on the third postoperative day, and the next x-ray (Fig. 5) demonstrates tubal patency one month after surgery. Pregnancy ensued during the next fertile period. The patient since has had a second normal pregnancy.

**CASE 2.—Failure.** Mrs. M. R. is a 34-year-old nurse, married four years with primary sterility. Work-up of the couple was negative except for bilateral tubal occlusion at the uterotubal junction. The first two x-rays (Fig. 6) demonstrate the first and last uterotubograms in a series of seven over a one-year period with failure to pass beyond the isthmic portion in any. At operation, a bilateral old pelvic inflammation was found with the tubes occluded and adherent in the anterior cul-de-sac. The right tube was completely occluded in the proximal third which was reimplanted under direct vision by bivalving of the uterus, as previously outlined. The left tube was probed open after the fimbria was circumcised, although it had been occluded throughout its entire length. The postoperative x-rays show passage of oil freely on the right which was reimplanted. The left tube which was probed open and circumcised failed to stay open. Failure to achieve pregnancy here is due probably to disorder of physiology subsequent to implantation of the right tube, whose rugae seemed normal but whose innervation may have been impaired in the resection and implantation. She does have a patent channel but its conducting function must be impaired. She is not pregnant as of one year following surgery.

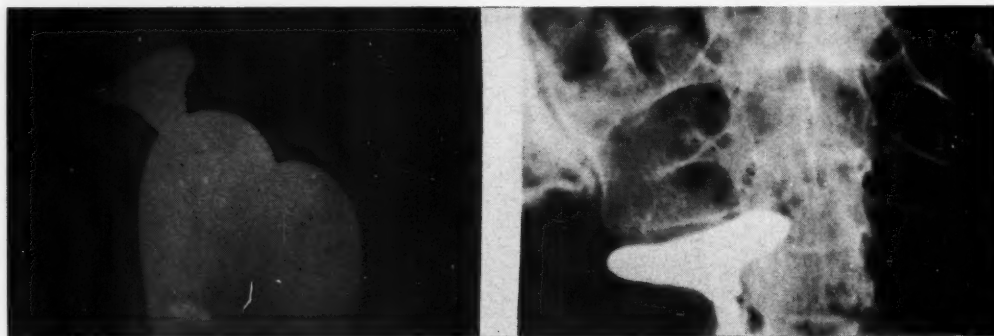


Fig. 7.—First and last uterotubograms over an eighteen-month period demonstrating complete occlusion at the uterotubal junction. The outer half of the right tube was reimplanted. The left tube was probed and irrigated open. Patient became pregnant first ovulation period after surgery, hence no postoperative uterotubograms can be submitted. Since it is impossible to determine if the pregnancy was consummated via the implanted or the nonimplanted tube, the latter must be given the credit.

*Interstitial Occlusion.—*

**CASE 1.—Success.** Mrs. D. W. is a 30-year-old housewife with a primary sterility of eleven years. Work-up of the couple was negative but for tubal occlusion. The panel of x-rays (Fig. 7) demonstrates the first and last uterotubograms over an eighteen-month period showing no improvement in the complete bilateral occlusion at the uterotubal junction. At operation, the right tube was closed for the proximal third, was probed open, and passed saline. The left tube was destroyed by old adhesions in the proximal half. This was resected and the normal distal half was reimplanted under direct vision by uterine bivalving. Air passed at 140 mm. of mercury on the third postoperative day. The patient became pregnant the first ovulation period following surgery, and no postoperative x-rays are available as a result. It is impossible to determine if the pregnancy was consummated via the implanted or the nonimplanted tube, therefore the latter must be given the credit.

**CASE 2.—Failure.** Mrs. M. R. is a 29-year-old housewife whose primary sterility was of ten years' duration. Check-up was normal except for a borderline count (40,000,000 after treatment with thyroid and vitamins) on the part of the husband, and many small subserous fibroids. The first x-ray (Fig. 8) demonstrated the best uterotubogram of five demonstrating ultimate passage to the fimbriae on this, the best. This could not be repeated on three subsequent attempts. At operation, there was bilateral occlusion of the proximal third of the tube, but patency beyond was normal with normal fimbriae. A multiple myomectomy was done with bilateral resection and implantation of the outer two-thirds of the tubes under direct vision. After operation, air passed bilaterally at 200 mm. of mercury on the third day. The postoperative uterotubogram demonstrates free flow with normal tubal architecture. The husband is questionably adequate as a partner. At the end of a year, an adoptive child was given to relieve emotional pressure. Efforts now are under way using the donor technique. Failure here may be on the husband's side.



Fig. 8.—Best uterotubogram of five demonstrating ultimate passage to fimbriae on this, the best, but could not be repeated on the last three attempts.

Postoperative uterotubogram demonstrating bilateral free flow with normal tubal architecture. Husband unquestionably adequate partner. Have adopted child, meanwhile having uterotubograms at three-month intervals. Possible ultimate artificial insemination.

#### *Complete Obstruction.—*

Three patients have been studied in this group, two of whom had had previous bilateral salpingectomy and the other a tubal ligation. No successes are noted, and for obvious reasons no x-rays are presented. The Estes' technique with slight modification has been followed. The writer is to be criticized for having implanted only one ovary in each case, thus diminishing by some percentage the chances of intrauterine ovulation each month. With more sober consideration, his fear of cystic degeneration of the ovaries in their new site may be unfounded, since the original disease process requiring sacrifice of the tubes may cause later cystic degeneration of the ovaries in a high percentage of cases. No attempt is made to review the literature on this procedure, but good results are given in from only two to four per cent of the reported cases. The laparotomy may be defended by the specific request of the patient for an accurate survey of the tubal status. This is possible only by laparotomy.

#### **Results of Study**

In all, 43 patients were operated upon, 27 of whom were primary sterility patients, and the remaining 16 were secondary. These latter cases included past spontaneous abortions, ectopic pregnancy, traumatic abortions, or term pregnancies. Effort was made to establish the etiology of the tubal occlusion by history, but results were remarkably unsatisfactory. Very few of the patients vouchsafed a story of past gonorrhea, infection after abortion (spontaneous or induced), or knew of complications following normal pregnancy. These patients all were private patients and not clinic-type.

It was interesting that of the 27 primary sterility cases, only seven gave a specific history of pelvic infection of any kind. It is difficult to evaluate the possible role of the cyclic shedding of the tubal epithelium, possible inspissation of such slough with resultant tubal occlusion. The role of the trichomonas is little known. Very likely the majority of the inspissations are relieved by insufflation methods without there being an adhesive element present. At any rate, one returns to gonorrhea, infection following pregnancies of varying kinds, pelvic pneumococcal infections, occlusions secondary to appendicitis, secondary to cervicitis, and then to an unknown wastebasket of etiological factors.

Of this group, sterility was associated with clinical pelvic inflammation in four cases although in the chronic stage, with endometriosis in two cases, with fibroids in three cases, and with ovarian cysts in two cases. However, all of these cases were screened by air and oil insufflations before surgery. Where malignancy was suspected, or where disordered bleeding or increasing pelvic masses were found, surgery was done immediately. These latter cases are not included in this study.

The results are summarized in Table I.

TABLE I

<i>Number of cases</i>	43	
Primary sterility	27	
Secondary sterility	16	
<i>Types of Obstruction</i> (Classified as the optimum penetration of oil by a minimum of three uterotubograms repeated at monthly intervals)—		
1. Perisalpingitis	7 cases	4 successes
2. Fimbrial occlusion	16	11
3. Isthmic occlusion	11	4
4. Interstitial (uterotubal junction)	6	2
5. Complete (tubes previously sacrificed or requiring removal with implantation of ovary)		0
	43 cases	21 successes
<i>Successes</i>	21	or 48.8 per cent
Spontaneous abortions	2	
Ectopic pregnancies	0	
Viable pregnancies	19	or 44.1 per cent
Premature deaths	1	corrected survival rate 41.8 per cent
<i>Average months after surgery to achieve pregnancy</i>	7.4	
<i>Deaths</i>	0	

### Summary

It would suggest that surgery has its place in the treatment of tubal occlusion where nonsurgical efforts are of no avail after conscientious and prolonged therapeutic effort has been given. In this series, the best results came in those cases where the least had to be done, as in simple lysis of peritubal adhesions, and next best in uncomplicated closure of the fimbriae. Where there has been disorder of mucosal pattern, impaired blood supply, or where the surgical procedure itself may disorder tubal innervation, results justifiably are poor. The reimplanted segment of tube or the unsupported ovary moored in the uterine wall would give the least good results, admittedly.



The justification for surgery then is simple. If all nonsurgical efforts are of no avail, then the patient is given a choice of adoption or of exploratory laparotomy. Earlier efforts to answer these things by peritoneoscopy and culdoscopy were woefully inadequate. Exploratory laparotomy it must be, for only upon careful palpation of the tube, with evaluation of its potential (as well as that of the ovary) can proper surgical correction be undertaken. Adequate chemotherapy and antibiotic therapy must be employed. Finally, meticulous aftercare to insure continued patency of the tubal canal during the healing period must be done, night or day, fair wind or foul. This latter cannot be overemphasized.

In this day of "semi-adoption" procedures, or artificial insemination, more liberty may be taken in surgical attack, either upon the female or the male. These couples are usually well deserving, for they have selected themselves as desirable by their untiring efforts to have a child of their own often long before they have appealed to the sterility expert. However, the male factor must have been evaluated and dispelled *before* surgery and not as a puzzled postoperative routine.

### Conclusions

1. A series of 43 cases of primary and secondary sterility unrelieved by persistent pressure methods is presented.
2. Success in securing pregnancy through surgical effort is graded directly by the amount of disorder of tubal function, of circulation, or of innervation.
3. The hopefulness or hopelessness of the situation can be evaluated only by exploratory laparotomy, if all other factors are normal or corrected. The patient must have an honest and careful recitation of the statistics of failure and of operative loss in advance.
4. Persistent and conscientious aftercare is as important as the proper selection and execution of the surgical technique in continued relief of tubal occlusion. This must begin two or three days after surgery and must follow until pregnancy is achieved.
5. Roughly, four in ten patients so selected may have a child. The remainder at least have the consolation of trying every channel before adoption is undertaken.
6. No successes are reported from implantation of the ovary in the uterine wall.

## TREATMENT OF THE MENOPAUSE

WILLIAM H. PERLOFF, M.D., PHILADELPHIA, PA.

(From the Union Health Center)

A LARGE number and variety of therapeutic agents are advocated for the relief of the symptoms of the menopause. This study was undertaken in order to compare the effects of some representative types of such medications on symptoms and vaginal smears of menopausal patients.

### Characteristics of Clinical Series

Two hundred women in whom a clinical diagnosis of the menopausal syndrome was made form the subject of this study. They are members of the Union Health Center, a clinic established to provide medical care for the Philadelphia members of the International Ladies' Garment Workers Union. The general economic, social, and cultural level of this group is perhaps more uniform than that seen in the average clinic and private practice. Each patient had had a thorough medical and gynecological evaluation prior to referral to the endocrine clinic.

TABLE I

AGE	NUMBER OF PATIENTS	PER CENT OF 200 PATIENTS
24-29	4	2.0
30-39	14	7.0
40-49	100	50.0
50-59	79	39.5
60	3	1.5

Age distribution, according to decades, is shown in Table I. Onset of symptoms predated this study by three to five years, on the average. Of the 200 patients, 115, or 57.5 per cent, were married and were living with their husbands. The others were either single, separated, or widowed. No correlation between marital status and severity of symptoms was apparent.

TABLE II

MENSTRUAL STATUS	NUMBER OF PATIENTS	PER CENT OF PATIENTS	AVERAGE AGE
Regular	19	9.5	44.0
Irregular	44	22.0	46.2
Amenorrhea	137	68.5	48.2
Natural	78	56.9	49.7
Artificial	59	43.1	46.4
Panhysterectomy	47	79.7	47.0
Oophorectomy	6	10.15	40.8
Radium	6	10.15	48.8

Table II shows the menstrual status of our patients. Sixty-three were still menstruating, nineteen regularly. Fifty-nine had had an artificially induced menopause, fifty-three by surgical means and six by radiation. The

average age of the nineteen regularly menstruating women was 44 years, 5.7 years lower than that of women with naturally occurring amenorrhea and patients with irregular menses were, on the average, 3.5 years younger than the group with amenorrhea. It would appear, therefore, that symptoms of the menopause may precede disturbances of the menses by at least two years and that complete amenorrhea may be expected in only two-thirds of patients with climacteric symptoms.

Ninety-two and five tenths per cent of patients complained of hot flushes and 50 per cent of headaches. All patients presented symptoms of flushes and/or headaches. The incidence of symptoms is shown in Table III. Qualitative differences in presenting symptoms between patients with artificially induced and naturally occurring menopause were not observed.

### Drugs

It is impractical to study all the preparations available, so that only representative members of each of the large classes were employed. Diethylstilbestrol was not included because it has already been carefully studied, and detailed information concerning its pharmacology and therapeutic effectiveness is in the literature.<sup>1, 2</sup>

The therapeutic agents selected for study are as follows: alpha-estradiol (Progynon-DH), oral; alpha-estradiol benzoate (Progynon-B), parenteral; alpha-estradiol pellet, subcutaneous; bisdehydrodoisynolic acid, oral; 3-4 bis (m-methyl-p-propionoxyphenyl)hexane (Meprane), oral; 4:4'dehydroxy-alpha-delta-diphenyl-beta-delta-hexadiene (Dienestrol), oral; ephynal acetate (Ephynal Acetate), oral; estrone, parenteral; ethinyl estradiol (Estinyl), oral; methyl-bisdehydrodoisynolic acid, oral; mixed conjugated estrogens-equine (Premarin), oral.

TABLE III

SYMPTOMS	ALL PATIENTS (200)		NATURAL MENOPAUSE (141)		ARTIFICIAL MENOPAUSE (59)	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Flushes	185	92.5	128	90.8	57	96.6
Headaches	100	50.0	69	48.9	31	52.5
Nervousness	45	22.5	33	23.4	12	20.3
Depression	43	21.5	27	19.1	16	27.1
Fatigue	24	12.0	17	12.0	7	11.8
Dizziness	23	11.5	18	12.7	5	8.4
Insomnia	20	10.0	13	19.2	7	11.8
Vague pains	13	6.5	10	7.1	3	5.1

### Methods

Only patients whose symptoms could clearly be ascribed to the menopausal syndrome were included in this series. Psychotherapy, other than that consequent to the dispensation of medication, was avoided in order to eliminate the factor of variable suggestion. Interviews were short and patients were kept to a fairly strict question and answer routine.

In order to minimize hangover effects of one drug upon another, visits were spaced at five- to six-week intervals. The dose of each medication was adjusted until the minimum effective dose was obtained. This was considered to be achieved when all symptoms were relieved, but the patient continued to experience an occasional, fleeting and mild flush. The patient was then given

TABLE IV

MEDICATION	NUMBER TREATED	NUMBER COM- PLETELY RELIEVED	PER CENT COM- PLETELY RELIEVED	NAUSEA		BLEEDING			RELATIVE COSTS OF ORAL PREPARATIONS (EXPRESSED) AS MULTIPLES OF ESTINYL AND DIENESTROL
				NUMBER	PER CENT	INCIDENCE IN ALL PATIENTS	INCIDENCE IN PATIENTS WITH AMENOR- RHEA	INCIDENCE IN PATIENTS CAPABLE OF BLEEDING	
Progynon-DH	81	68	83.9	3	3.7	8.7	6.2	9.6	11
Progynon-B	59	55	93.1	0	0	0	0	0	
Pellets—alpha estradiol	45	43	95.6	0	0	0	0	0	
Bisdehydrodoisynolic acid	24	4	16.6	3	12.5	8.33	4.16	8.33	
Meprane	64	52	81.5	4	6.25	29.7	21.9	33.9	2
Dienestrol	98	90	90.8	6	6.1	17.2	7.15	20.7	1
Ephynal Acetate	65	17	26.1	1	1.5	1.5	1.5	1.8	15
Estrone	96	76	79.1	0	0	12.5	7.3	14.1	
Estinyl	138	130	94.2	13	9.4	23.2	14.5	27.6	1
Methylbisdehydrodoisyn- olic acid	35	14	40.0	4	11.4	5.7	5.7	6.9	
Premarin	95	91	95.8	4	4.2	11.6	7.4	12.3	4



a new drug and the procedure repeated. The order of administration was varied from patient to patient and in the same patient in order to minimize seasonal effects and the influence of previous medication. In many instances, the minimum effective dose of a substance was prescribed at a later date in order to verify its accuracy.

Vaginal smears were taken at each clinic visit. Slides were prepared in duplicate, one stained according to the method of Shorr,<sup>3, 4</sup> the other, following the technique of Papanicolaou.<sup>5</sup> Smears were read without information concerning the clinical picture. Comparison of vaginal smear changes with variations in the clinical response was not made until completion of the study. Only those cases in which the diagnosis of cancer was suspected were discussed.

### Results

The comparative effects of therapy, incidence of nausea and bleeding, and relative costs of the preparations used are shown in Table IV. With the exception of Ephynal Acetate, bisdehydrodisynolic acid and its methylated form, 80 per cent or more of patients were relieved completely of symptoms by all the drugs employed. Although many patients showed partial response to Ephynal Acetate, bisdehydrodisynolic acid and its methylated form, complete relief was not obtained in most instances. This may be due to insufficient dosage.

In a study of this kind, it is difficult to achieve adequate levels of each drug in every patient because of the complicating effects of nausea, bleeding, and patient resistance. Following complete control of symptoms with one preparation, change to another was occasionally refused. Furthermore, if the new drug was given in insufficient amounts, it was not unusual for the patient to object to an increase, attributing the return of her symptoms to the medication itself rather than to the inadequacy of the dose. Since the minimal effective dose was not always attainable, response to therapy was estimated on the basis of patients who had obtained complete relief of symptoms. Dose equivalents are listed in Table V.

TABLE V

PER CENT COMPLETELY RELIEVED	DOSES (ONLY DOSES USED IN THIS STUDY ARE CHARTED)				
	PROGYNON-DH	MEPRANE	DIENESTROL	ESTINYL	PREMARIN
0-9					
10-19			0.2		
20-29				0.02	0.625
30-39		1.0			
40-49				0.025	
50-59	0.5	2.0			
60-69			0.5		1.25
70-79					
80-89			1.0		
90-99	1.0	3.0	1.5	0.05	2.5

The incidence of nausea in this series is higher than that usually reported with estrogenic therapy. A drug was considered nauseating when its further use was refused by the patient and when the nausea could be elicited a second time at a later date. Notwithstanding these precautions, the incidence of nausea may be high because of the nature of the patients in this series. In

many instances, these women worked together in the same shop. Symptoms and reactions to therapy were discussed by them at length, and negative suggestion was not counteracted by reassurance on the part of the interviewer. Nausea, as a presenting complaint, was usually relieved by estrogenic therapy.

One of the expected consequences of estrogen administration is endometrial proliferation. Uterine bleeding can hardly be called an untoward effect; nevertheless, it is a reaction one strives to avoid. Irregular uterine bleeding is common during the menopause, and Te Linde and Bennet<sup>6</sup> have pointed out that bleeding during estrogenic therapy may be coincidental. These investigators treated a series of control patients with phenobarbital; bleeding occurred in 6.3 per cent. This figure is higher than in their estrogen-treated group. Table IV shows a higher incidence of bleeding than is reported in most series. Bleeding occurred in eighty-nine of the one hundred fifty-three women with intact uteri. Sixty-six of these reported the presence of a bloody vaginal discharge, whereas twenty-three patients were unaware of bleeding. When bleeding is re-evaluated in terms of therapeutic episodes, each of five to six weeks' duration, the incidence is seen to be much less impressive (Table VI).

TABLE VI

	REPORTED		NOT REPORTED		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Bleeding patients	66	33.0	23	11.5	89	44.5
Bleeding episodes	92	6.05	26	1.7	118	7.75

The study comprises 1,520 therapeutic episodes.

In view of the long duration of this experiment, the high incidence of bleeding on a patient basis is to be expected. Moreover, the character of the study was unavoidably such that the optimum conditions for the development of uterine bleeding were created. As soon as the minimal effective dose of any medication was determined, a new material was dispensed. Because this was frequently started in subtherapeutic dosage, an estrogen-withdrawal effect was produced. This serial administration of drugs makes bleeding very hard to interpret. Doris Phelps<sup>7</sup> maintains that endometrial activity may be influenced by hormonal effects operating several cycles prior to the one in question.

Comparative costs are shown in Table IV. Cost calculations were made on the basis of the maintenance dose required by 100 per cent of relieved patients, and are expressed in multiples of the cost of Estinyl and Dienestrol, which were the most economical of the preparations used.

### Analysis of Therapeutic Agents

Alpha-estradiol (Progynon-DH) is probably identical with the follicular hormone. It is the dehydroxyestrin, resulting from the reduction of keto-hydroxyl estrin (estrone) to a secondary alcohol. It is expensive and 80 to 90 per cent of its potency is said to be lost on passage through the stomach.<sup>8</sup> It appears to be most useful when cost is unimportant and when side reactions to other oral estrogenic preparations develop. Eighty-three and nine tenths per cent of patients treated with doses not exceeding 1.5 mg. were completely relieved. The incidence of nausea and bleeding was lower than with any other estrogen and the sense of general well-being following adequate dosage was pronounced.

Alpha-estradiol benzoate (Progynon-B) is the ester of alpha-estradiol. Esterification plus suspension in oil prolongs its effectiveness without decreasing its potency. Patients were well maintained on weekly doses of Proynon-

on-B, although in some series injections were required every three<sup>9</sup> to five days.<sup>10</sup> Neither bleeding nor nausea was reported, although many patients were maintained on it for as long as three months. Control of symptoms was readily achieved and weekly maintenance doses of 0.33 to 0.66 mg. kept patients asymptomatic.

Alpha-estradiol pellets are crystals of alpha-estradiol compressed into 25 mg. cylinders. Forty-three patients received an implant of 25 mg. and two patients, because of their previous high estrogenic needs, were given two pellets (50 mg.). Forty-three of these forty-five patients were completely relieved of symptoms. Of the two failures, one was a patient who required four times the usual dose of other estrogens. Her theoretical need was for three to four pellets, but she was given two and was only partially relieved. The other patient considered this therapy unsuccessful because of the persistence of headaches, although her flushes disappeared. Her headaches were not menopausal in character; however, because of the equivocal nature of the response, this patient was classified as a failure.

All other patients heartily endorsed this form of therapy. Only women who had been hysterectomized received pellet implantation. Occasionally, evanescent breast pain was reported. No other untoward reactions were observed. The duration of therapeutic response seems to be from four to eight months with an average of six months.

Pellets containing alpha-estradiol,<sup>11</sup> alpha-estradiol benzoate,<sup>12</sup> alpha-estradiol dipropionate,<sup>13</sup> estrone,<sup>6, 14</sup> diethylstilbestrol,<sup>6</sup> and crystalline estrogens from pregnant mare urine<sup>15</sup> have been successfully employed by others. The paucity of untoward reactions to this form of therapy has been repeatedly observed,<sup>11, 13, 14, 15</sup> although Twombly<sup>16</sup> noted a rather high occurrence of breast changes (50 per cent of cases), cervical leucoplakia, and increase in size of pre-existing myomas. Because of the reported high incidence of uterine bleeding,<sup>11, 16</sup> the use of these pellets should be reserved for patients who have had a hysterectomy. The implantation of a pellet in a woman at the time of panhysterectomy may possibly prevent the abrupt onset of menopausal symptoms.

No information as to cost can be given since pellets of alpha-estradiol are not yet commercially available.

Bisdehydrodisynolic acid is synthetic dl-1-ethyl-2-methyl-7-hydroxy-1,2,3,4-tetra-hydro-2-phenanthrene carboxylic acid, an oxidative derivative of d-equinalin. It and its methylated derivative have been used extensively in Europe.

This material is not commercially available and therefore has no price listing. Its use in Europe indicated that it was a potent, well-tolerated drug producing all the physiologic effects of estrogen.<sup>17, 18</sup> Its use in doses of 0.1 to 0.3 mg. gave complete relief to 16.6 per cent of patients and partial relief to an additional 33.2 per cent. In no instance did the beneficial effects of therapy persist longer than twenty-eight days after the medication was withdrawn. Nausea developed in three, and abdominal pain in two of twenty-four patients. Two patients complained of vaginal spotting.

In the doses used, bisdehydrodisynolic acid appeared to be relatively inefficient in controlling menopausal symptoms. The incidence of nausea was great and claims made for this drug could not be substantiated.

3-4-bis(m-methyl-p-propionoxyphenyl)hexane (Meprane) is a synthetic compound more closely related to the diethylstilbestrol series than to the naturally derived estrogens. This material was used in doses not exceeding 3 mg. daily and completely relieved the symptoms of 81.5 per cent of patients treated. The incidence of nausea was relatively low, comparing well with Dienestrol in this regard. Lin<sup>19</sup> likewise noted this tolerance to the drug.



In our series, however, bleeding was more frequently associated with the use of Meprane than with any other preparation. Since the vaginal smear responses following its use were no more pronounced than with other potent estrogens, we believe that the effect on the endometrium suggested by our figures for bleeding are open to question. Meprane is an economical, well-tolerated, and potent estrogen which may have a useful place in the therapy of the menopause and deserves further investigation with regard to the production of bleeding.

4:4'dehydroxy-alpha-beta-delta-hexadiene (Dienestrol) is related chemically to diethylstilbestrol. It is a potent estrogenic material which is in the same general economic classification as Estinyl. All reports on this material suggest that the incidence of untoward reactions is low. Barnes<sup>20</sup> treated a group of thirteen, and Rakoff, Paschkis, and Cantarow<sup>21</sup> a group of forty menopausal women without producing nausea in a single case on any dose. Sikkema and Severinghaus<sup>22</sup> found the material to be free of nauseating effects in doses of less than 0.5 mg. whereas Finkler and Becker<sup>23</sup> reported nausea in 4.3 per cent of their seventy patients.

In general, atrophic vaginal smears showed the expected estrogenic effect coincident with control of symptoms. This correspondence was noted by Finkler and Becker.<sup>23</sup> Rakoff, Paschkis, and Cantarow,<sup>21</sup> however, report that "the dosage necessary to obtain a vaginal smear response was in most instances considerably higher than the dosage necessary to obtain a good clinical response." In this study the vaginal smear response produced by Dienestrol paralleled very closely that observed in patients treated with Estinyl and Meprane. This was particularly noticeable when these drugs were administered in effective doses to the same patient in turn.

Of ninety-eight patients treated with Dienestrol, 90.8 per cent showed complete relief of symptoms. Ninety per cent of these were maintained on daily doses of 1.0 mg. or less. Dienestrol exhibits potency, ease of administration, relatively low incidence of side reactions, and economy, which makes it a valuable agent for the therapy of the menopause. The general sense of well-being, however, is not marked. This was reflected in the small percentage of patients who specified preference for Dienestrol over other preparations.

dl-alpha-tocopherol acetate (Ephynal Acetate) is the synthetic acetic ester of vitamin E which possesses biological potency equal to the purified naturally occurring vitamin. The rationale for the use of this material in the menopause is not clearly established. It is said that derangement of gonadotropic activity may be associated in some cases with vitamin E deficiency.<sup>24</sup> The steroid nature and chemical configuration of this substance may bear some relation to its purported effects in the menopause. It completely relieved the symptoms of 26.1 per cent of sixty-five patients with doses of 75 and 150 mg. daily. The effect of still larger doses appears to deserve study, since many patients who had been refractory to the lower dose responded to the higher one. Although incompletely relieved, another 26 per cent were improved with doses up to 150 mg. The question of dosage is still equivocal, however, for Hain and Sym<sup>25</sup> reported response to 12 mg. of tocopherol daily and Christy<sup>24</sup> achieved satisfactory relief in twenty-three of twenty-five patients with 10 to 30 mg. daily.

Notwithstanding the large doses used, Ephynal Acetate produced slight nausea in only one patient. No gross bleeding was reported but microscopic bleeding was observed in one case. The presence of blood in this patient's vaginal smear was likely unrelated to the effects of therapy. Even transitory suggestions of toxicity were absent. Ephynal Acetate exerts no significant effect upon the vaginal smear.



Ephynal Acetate is an expensive preparation. Its role in the therapy of the menopause has still to be established. Its apparent freedom from toxicity makes it a potentially valuable agent for the treatment of the menopausal patient who bleeds easily with estrogens. It does not appear to act as a placebo since inadequate quantities of other drugs caused return of symptoms in patients who had been effectively controlled with Ephynal Acetate.

Estrone is a ketohydroxy estrin derived from urine, usually from the urine of pregnant mares. It is an excretory metabolic product of alpha-estradiol. In the majority of patients, 0.4 to 1.0 mg. each week was the effective maintenance dose. Bleeding occurred occasionally, but continuous therapy was often given over a period of many months. No other untoward effects were reported. Estrone is a moderately costly estrogenic preparation which is neither as effective nor as prolonged in action as alpha-estradiol benzoate.

Exact biological comparison of estrone and alpha-estradiol benzoate is difficult. This was recognized by The League of Nations Health Organization, and this Council recommended that biological units be abandoned and that relative potencies be discussed in milligrams. Clinically, one rat unit appears to be the equivalent of ten international units and relative doses of estrone and alpha-estradiol benzoate may usually be determined in this way. Patients differ so radically in their relative responses to these two materials, however, that one must not expect this ratio to hold in all instances.

Ethinyl estradiol (Estinyl) is a potent relative of alpha-estradiol with an ethinyl group on the 17-carbon atom of the phenanthrene nucleus. It is about five times as effective as parenteral alpha-estradiol but approximately 25 times more potent than oral alpha-estradiol.<sup>8</sup> It is the most potent estrogen available and it produces its pharmacological effects in smaller doses than any other drug known. It is one of the two most economical materials used in this study. Ease of administration was apparent in that 94.2 per cent of all patients were completely relieved. Ninety-six per cent of these required no more than 0.05 mg. daily for satisfactory maintenance.

Nausea was produced more frequently with this drug than with any other (9.4 per cent), and bleeding was a common complication. Nevertheless, when clear-cut subjective preference to any drug was voiced, Estinyl was more frequently preferred than any medication, excepting Premarin which led by a slight margin. Estrogenic effect on the vaginal smear was usually commensurate with improvement of symptoms. The economy of Estinyl, coupled with its ability to produce rapid relief of symptoms makes it a particularly useful medication for the routine therapy of the menopause.

Methylbisdehydrodisynolic acid (methyl ester, dl-1-ethyl-2-methyl-7-hydroxy-1,2,3,4-tetrahydro-2-phenanthrene carboxylic acid) was used in doses of 0.05 to 2 mg. daily and gave complete relief to 40 per cent of patients treated. However, seven of the fourteen women relieved had mild pretreatment menopausal complaints. Its pharmacologic and biologic activity is similar to the previously discussed bisdehydrodisynolic acid.

The high incidence of nausea (11.4 per cent) and the low therapeutic response are not in keeping with the reports of European investigators. The results with methylbisdehydrodisynolic acid are, in general, similar to those observed with the demethylated form and together suggest that the usefulness of the materials may be less than originally believed.

Premarin (mixed conjugated estrogens) is derived from the urine of pregnant mares and contains a mixture of the excretory products of alpha-estradiol as well as small amounts of other estrogens of equine origin. Sodium estrone sulfate is the major component of this preparation. It is four times

as costly as the most economical preparations used. Apart from cost, this material appears to have advantages over many of the oral estrogens. Ninety-five and eight tenths per cent of patients treated with 3.75 mg. or less daily obtained complete relief of symptoms. This satisfactory response has been noted by other workers.<sup>26, 27</sup> Progynon-DH is the only oral estrogen which produced less nausea and bleeding than Premarin. General tonic effects were noteworthy and the greatest percentage of patients who expressed clear-cut preferences for any drug designated Premarin. This estrogen appears to be moderately effective in promoting cornification of the atrophic vaginal smear.

### Symptomatic Response to Therapy

Response to therapy was frequently dramatic with disappearance of all symptoms occurring simultaneously. When relief was more gradual, certain symptom relationships were noted. Headaches appeared to remain more refractory to therapy than flushes and often required larger doses for complete relief. Alleviation of insomnia appeared to parallel closely relief of flushes. Although excellent response was noted in many cases, nervousness and depression were the most resistant of all symptoms to therapy. The administration of larger doses of drugs to effect control of these symptoms was not attempted. Vague bone and joint pains, paresthesias and other miscellaneous symptoms were often relieved with adequate doses of medication.

Certain patients, whose symptoms appeared to be adequately controlled, complained of return of headaches and/or flushes at regular intervals. Questioning revealed that these episodes corresponded with the times of the expected menses. This phenomenon occurred in patients who had had pan-hysterectomies and in whom the presence of ovarian tissue was most unlikely. Increasing the dose of estrogen usually suppressed these cycles. This periodicity obviously cannot be ascribed to the ovary in these patients and some other explanation must be considered. In this connection, the possible roles of the adrenal and the pituitary come to mind. The rhythmic increase in pain and nodularity in the breasts of some untreated oophorectomized women is also of interest.

Every patient could be completely relieved of her menopausal symptoms by one or another of the oral preparations administered.

### Vaginal Smears

In this series of two hundred patients, no smears were found which were positive for cancer. Two were considered suspicious but investigation with dilatation, curettage, and cervical biopsy revealed an endometrial polyp in one case, whereas no pathology could be demonstrated in the second. When smears were atrophic, primitive and even bizarre cells were occasionally observed. The administration of estrogen always eliminated doubt as to the character of these cells.

Failure to find genital cancer in this group of two hundred menopausal women may be attributed to the fact that periodic examinations and prophylactic therapy of precancerous lesions of the pelvic organs are routine. All patients must be given clearance by the Gynecological Department before they are referred to the Endocrine Department for therapy of their menopausal symptoms.

Because of variation in the production of estrogen by the ovaries of menstruating women, changes in the vaginal smear were not consistent with the type or amount of therapy; therefore, smears of amenorrheic patients only were used to interpret treatment responses.

Control smears of patients with amenorrhea showed 24 per cent to be of the atrophic variety (Grade I, preponderance of basal or deep cells and abundant polymorphonuclear leucocytes); 45 per cent were of the moderately severe type (Grade II, deep cells, variable numbers of epithelial cells and polymorphonuclear leucocytes); 12 per cent showed slight estrogen deficiency (Grade III, predominance of noncornified epithelial elements, rare deep cells and occasional polymorphonuclear leucocytes); and 19 per cent showed full estrogen effect (Grade IV, with predominance of cornified cells, rare polymorphonuclear leucocytes and little mucus).

In general, flushes were of greatest intensity in patients with vaginal smears of Grades I and II and less prominent in Grades III and IV. Frequent exceptions were seen, however. Although the vaginal smear may be of occasional value in an equivocal case, its routine application for diagnosis and evaluation of therapy in the menopausal woman is unnecessary. It does, however, enable the physician to detect microscopic bleeding. In accordance with the experience of other investigators<sup>14, 19</sup> vaginal smear response to therapy in this series showed no necessary correlation with symptomatic relief. There appeared to be, however, more correlation between the clinical response and the vaginal smear than between the smear and the dose of medication employed.<sup>7</sup> After satisfactory relief of symptoms with any of the estrogens employed, a much greater increase in the dose was required to improve further the vaginal smear.

Analysis of the influence of each medication on the vaginal smear was performed in two ways. The relative effects of different medications in the same patient were compared with the average effects of various medications in different patients. These two methods of analysis showed fairly close agreement.

Estinyl, Dienestrol, and Meprane produced similar vaginal smear changes in the same patients and caused the same general range of response in different patients. In decreasing order of effect were Premarin, alpha-estradiol pellets, methylbisdehydrodisynolic acid and Ephynal Acetate.

### Summary

Two hundred women with a clinical diagnosis of the menopausal syndrome were studied. These women were treated with a variety of medications advocated for the therapy of the menopause. Response of symptoms and vaginal smears were determined. The incidence of undesirable effects was also noted. On the basis of these evaluations a comparison of the various medications used is presented.

### Conclusions

1. No single oral medication used in this study was universally effective in relieving menopausal complaints without the production of undesirable side effects.
2. It was possible, however, to relieve menopausal symptoms in all our patients by the oral administration of one or another of the preparations employed.
3. No deleterious effects may be anticipated as a consequence of estrogenic therapy providing the patient is under constant, careful supervision.
4. Although the vaginal smear may often be correlated with the symptom response, many exceptions exist and it appears to have little value for routine use. Occasional vaginal smears should be taken at intervals to detect microscopic bleeding.

5. Although hysterectomized women may be well controlled with oral medication, most of our patients preferred alpha-estradiol pellet implantation.

### Acknowledgments

This study was aided by grants from the Union Health Center, International Ladies' Garment Workers Union for Philadelphia and Vicinity, Hoffmann-La Roche, Inc., and Reed and Carnrick.

The author wishes to thank the following persons and companies for the liberal supplies of substances:

Drs. Edward R. Neary and J. A. Dailey of the White Laboratories, Inc., for Dienestrol; Drs. William T. Strauss and R. J. Floody of Hoffmann-La Roche, Inc., for Ephynal Acetate; Drs. William H. Stoner and Edward Henderson of Schering Corporation for Estinyl, bisdehydrodoisynolic acid, methylbisdehydrodoisynolic acid, Progynon-B, alpha-estradiol pellets, and Shorr stain; Dr. Ralph A. Perkins of Reed and Carnrick for Meprane; Dr. J. Murray Scott of Ayerst, McKenna & Harrison for Premarin; and Dr. Katherine Kuder of the Ortho Pharmaceutical Company for the Papanicolaou stains.

All vaginal smears were taken and read by Dr. Mary B. Dratman.

The author wishes to express his thanks to Dr. Joseph A. Langbord and Mr. Isidor Melamed of the Union Health Center for their cooperation and to Dr. Edward Rose of the University of Pennsylvania Hospital for reviewing this manuscript.

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## A REPORT ON COMPARATIVE STUDIES OF NEWER DRUGS USED FOR OBSTETRICAL ANALGESIA

E. J. SMITH, M.D., AND S. F. NAGYFY, M.D., IOWA CITY, IOWA

*(From the Departments of Pharmacology and Obstetrics and Gynecology, State University of Iowa College of Medicine)*

THESE studies\* were undertaken to determine the clinical suitability of certain new analgesic drugs for pain relief during labor.

1, 3, dimethyl-4-phenyl-4-propionoxy piperidine hydrochloride, Nisentil, a short-acting compound given the serial number Nu 1196 was the principal object of this investigation. The chemical synthesis and the pharmacologic action of this drug have been described by Ziering and Lee,<sup>1</sup> Holland and Gross,<sup>2</sup> and Randall and Lehmann.<sup>3</sup> Morphine, Methadon, and combinations of morphine with Prostigmine or scopolamine were also employed.

### Methods

The clinical estimation of analgesia during labor is difficult because of numerous variable factors. Consequently, all observations were made by one person in order to secure an evaluation largely devoid of the personal equation. As a control on the observations of this individual the reactions of the patient and of the attending obstetrician with regard to the effectiveness of the analgesia were considered. If these all agreed that labor pains were appreciably eased, the drug effect was considered good. Failure of the drug to produce the desired result was readily apparent, but evaluation of the effect as fair or indifferent was difficult. Patients vary widely in their tolerance to visceral and somatic pain. Many patients can be kept fairly comfortable during the first stage of labor with almost any available analgesic drugs, but during the expulsive phase of the second stage greater analgesia is required than can be given without jeopardizing the fetus. Consequently, it becomes necessary to administer supplementary anesthetic agents by inhalation or injection to keep the patient comfortable and permit whatever delivery procedures may be indicated. None of the results could be considered excellent because perfect analgesia was obtained only by the supplemental administration of gaseous anesthetics or the use of regional block, e.g., caudal and spinal anesthesia.

Records were kept on "Keysort" cards which facilitated the collection and comparison of data. The information thus obtained was then critically graded and tabulated on a large chart, significant portions of which are included in this report. Some selection of cases was employed early in the study, in that only essentially normal obstetric patients were used. Later, after no untoward effect of the drug had been noted, only those patients were excluded in whom the drug was not given as directed, or was given too late in labor to have any effect.

Observations were first made on the effects of morphine in order to establish a base line for comparison of the effects of the other drugs.

The first series studied included twelve patients receiving morphine sulfate according to the following schedule:

\*Supported in part by a grant from Hoffmann-La Roche, Inc.

1. *Morphine sulfate* grain 1/6 (.01 Gm.): The first dose was given when labor pains were strong and regular, or when the cervix was approximately 4 cm. dilated. Subsequent doses were given as necessary, but not more frequently than every three hours. One half of the dose was administered intravenously (grain 1/12 — .005 Gm.) and the rest subcutaneously, or all subcutaneously, depending upon the need for analgesia.

2. *Atropine sulfate* grain 1/100 (.6 mg.): This was given intravenously 10 to 15 minutes prior to expected delivery, principally to facilitate administration of the inhalation anesthesia.

3. *Anesthesia for delivery*: Nitrous oxide or cyclopropane was employed as needed. In the latter part of the series regional block anesthesia was employed to eliminate the respiratory depressant effect of inhalation anesthetics.

In order to obtain more data on the effects of morphine without supplemental inhalation anesthesia, forty-two patients were given morphine alone by the following schedule:

1. *Morphine sulfate* in doses of grain 1/8 (.0081 Gm.) was given intravenously when labor was definitely established and thereafter at the discretion of the obstetrician.

2. *Atropine* was given as before.

3. *Anesthesia for delivery*: As many women as possible were delivered under regional anesthesia.

The results obtained compared favorably with previous investigations carried out by Mengert in 1941.<sup>4</sup>

The second group included twenty patients who received morphine and Prostigmine according to the following schedule:

1. *Morphine sulfate* grain 1/6 (.01 Gm.): Given as in previous series.

2. *Prostigmine* (.5 mg.) intramuscularly: When labor was well established or cervical dilatation was approximately 4 cm., the total dose of morphine was repeated as necessary, but the Prostigmine was given not more often than every four hours.

3. *Atropine*: As before.

4. *Anesthesia for delivery*: Nitrous oxide and/or cyclopropane.

The dose of Prostigmine was limited because its effect upon the uterus is not known. However, there was no decrease in the average length of labor in this group. The analgesic effect of this combination was not materially different from that of the previous series. It was considered desirable to use this combination in view of Slaughter's<sup>5</sup> recent work indicating that the analgesic effect of morphine is enhanced by Prostigmine. He suggested that acetylcholine plays a part in the potentiation of the morphine effect. Results in this small series were not very conclusive.

The third group consisted of thirty-two patients in whom Methadon was used.

This drug is accredited with exceptionally good analgesic effects on experimental animals and it has been suggested as an agent which might have possibilities as an analgesic in obstetrics.<sup>6</sup> The first six patients were on the following schedule:

1. *Methadon* 5 mg. subcutaneously: The first dose was given as in previous schedules and repeated every 3 to 4 hours.

2. *Atropine sulfate* grain 1/100 (.6 mg.) also as before.

3. *Anesthesia for delivery*: As indicated.

This dosage was found to be inadequate and the initial dose was increased to 10 mg., followed by 5 mg. every 3 to 4 hours. Later, it was necessary to increase the dose to 10 mg., followed by 10 mg. every 1 to 2 hours because the

desired degree of analgesia was not obtained. Because of the poor analgesia and the prolongation of respiratory depression of the newborn, even with small doses, this drug was considered unsatisfactory for obstetric analgesia and the series was discontinued.

Nu 1196 was first used under the following schedule:

1. *Nu 1196* 10 mg. subcutaneously: The first dose was given when the patient was definitely in labor or when cervical dilation had reached approximately 4 cm. Subsequent doses were injected at one-hour intervals, as necessary. The final dose was not to be given during the last hour before delivery.

2. *Atropine*: As before.

3. *Anesthesia for delivery*: Regional or spinal anesthesia is preferred to inhalation agents, whenever feasible.

Because of the limited analgesic effect of 10 mg. of Nu 1196 the dose was gradually increased until 30 mg. every hour were given. At first an attempt was made to omit the administration of the drug within the last hour before delivery. Later, however, this precaution was abandoned in order to ascertain the time after an injection when the respiratory depressant action is most marked.

Nu 1196 was also given orally according to the following schedule:

1. *Nu 1196* 30 mg. orally, 15 mg. subcutaneously: The oral dose was given only to those patients from whom food had been withheld for several hours and who were definitely in labor. The 15 mg. subcutaneous doses were started at the same time or later, and were repeated every hour as necessary.

2. *Atropine*: As before.

3. *Anesthesia for delivery*: Saddle blocks were preferred, but regional or inhalation anesthesia was used occasionally.

The dose was later increased to 40 mg. orally and 20 mg. subcutaneously.

Nu 1196 was also given in 20 mg. doses with scopolamine in doses of 1/150 grains (.432 mg.) repeated two to three times to produce amnesia, at the discretion of the obstetrician. Nu 1196 was given at the same time or more often.

In the morphine-scopolamine group the patients received morphine and scopolamine in a similar manner.

### Results and Discussion

Side reactions were not severe in any group and were confined largely to nausea and emesis. Patients receiving Methadon occasionally complained of tingling in the area in which the drug was given. Nu 1196 seemed to have moderate hypnotic power while Methadon appeared to have none.

Analgesia was rated as indicated in Table I for the various drugs which are grouped alone or in combinations, and in some cases according to the amount and manner of administration.

As stated earlier, it was most difficult to be dogmatic about the degree of analgesia except in those cases designated "good." Accordingly, in interpretation of the results, the number of "good" cases is the significant factor. In those who received scopolamine the factor of amnesia made the determination of analgesia almost impossible and certainly unreliable.

Patients who received morphine and morphine-Prostigmine had the lowest percentage of "good" analgesia. Of the fifty-four patients receiving morphine, ten, or approximately 19 per cent, had "good" analgesia. Twenty patients received morphine and Prostigmine. Three, or approximately 15 per cent, had "good" analgesia. Of the thirty-two patients receiving Methadon, thirteen, or

approximately 41 per cent, had "good" analgesia. Fifty-two patients received Nu 1196 in 20 mg. or less doses subcutaneously. Twenty-one, or 40 per cent, had "good" analgesia. Sixty-seven patients received Nu 1196 in 30 mg. doses subcutaneously. Thirty patients, or approximately 45 per cent, had "good" analgesia. Oral Nu 1196 combined with subcutaneous dosage gives a lower percentage of "good" results, 5 patients out of twenty-four having "good" analgesia.

TABLE I

DRUG	NO. CASES	ANALGESIA		
		FAILURE	FAIR	GOOD
Morphine	54	8	36	10
Morphine and Prostigmine	20	0	17	3
Methadon	32	7	12	13
Nu 1196, 10-20 mg.	52	11	20	21
Nu 1196, 30 mg.	67	11	26	30
Nu 1196, oral and subcutaneous	24	7	12	5
Morphine and scopolamine	39	3	13	23
Nu 1196 and scopolamine	43	6	23	14

With any drug used in obstetrics, a factor probably of more concern than analgesia is the effect on the baby. In trying to evaluate these effects a number of other factors must be considered, such as antepartum and intrapartum complications, type of delivery, and anesthetics used. At the outset of this study, most deliveries were conducted under cyclopropane or nitrous oxide, or a combination of the two agents. Later, saddle block anesthesia was used more frequently. Therefore, for evaluating fetal depression, the patients have been divided into three groups: those delivered under regional or spinal anesthesia; those under inhalation anesthesia; and those under combinations of regional or spinal and inhalation.

Fetal depression was judged by the time of onset of spontaneous breathing, the degree of cyanosis, muscle tone, time required for revival of depressed babies, and methods employed for resuscitation (Table II). In final evaluation of the drugs, the time up to the onset of spontaneous breathing and the time required for resuscitation have been most significant.

Revival time was considered as that required to initiate good crying or breathing to the point where it was felt safe to leave the infant. Some babies who cried immediately became apneic later and took longer to arouse. Table II shows the various analgesic drugs and indicates the degree of respiratory depression of the fetus obtained in each group.

In the entire group there was a total of 324 mothers and 330 infants (including six sets of twins). One hundred eighty-six mothers (192 infants) received Nu 1196 either alone or with scopolamine. One hundred forty-three mothers received Nu 1196 alone.

Antepartum complications included three patients with hypertension, three with diabetes mellitus, five with pre-eclampsia, one in premature labor, one with chronic nephritis, one with syphilis, one with a congenital heart lesion (intraventricular septal defect), one with Friedreich's ataxia and one with a contracted pelvis.

Intrapartum complications included eight cases of prolonged labor. Three patients had retained placentas and resultant hemorrhages of over 600 c.c. These complications were scattered through the various groups and appeared to have no relation to the drugs used. The drugs did not tend to aggravate existing complications.



TABLE II

AGENT	NUMBER CASES	ANESTHESIA	SPONTANEOUS BREATHING				REVIVED (CRYING) AFTER							TOTAL NUMBER DE- PRESSED	
			1-15 SEC.	16-30 SEC.	31-60 SEC.	60 SEC.	1 MIN.	2 MIN.	3 MIN.	4 MIN.	5 MIN.	10 MIN.	15 MIN.		
Methadon	7	Regional	5		2						1				2
Methadon	16	Inhalation	12		2	2						1			4
Methadon	9	Regional + inhalation	4	2	3			3							5
Morphine and Prostig- mine	20	Inhalation	17	2			1	1	1				2	1	5
Morphine	18	Regional	10	3	4		1		1				2		3
Morphine	23	Inhalation	13	3	4	3			1		2	1	5	1	11
Morphine	13	Regional + inhalation	6	1	1	5		1					3	1	5
Morphine and scopol- amine	32m 33b	Inhalation	16	4	9	4		1	3	2	3	3	1	1	14
Nu 1196 and scopol- amine	12	Regional	6	2	4					1		1	2		4
Nu 1196 and scopol- amine	21	Inhalation	10	4	2	5				2			5	3	10
Nu 1196 and scopol- amine	10	Regional + inhalation	5	2	2	1			2			1			3
Nu 1196 10-20 mg.	32m 33b	Inhalation	16	8	5	4					1	1	3	1	6
Nu 1196 10-20 mg.	6	Inhalation + regional	3	1	1	1		1				1			3
Nu 1196 10-20 mg.	14	Regional	11	2		1							2		2
Nu 1196 30 mg.	37m 38b	Regional	25	4	5	4			2			2		1	6
Nu 1196 30 mg.	14b* 15m	Inhalation	10	2		2			1			1	2		4
Nu 1196 30 mg.	15m 16b	Regional + inhalation	12	1	2	1		1			1	1	1		4
Nu 1196 oral	15m 16b	Inhalation	10	1	4	1			3			1			4
Nu 1196 oral	9	Regional + inhalation	8		1				1			1	1		3
Methadon	32	All types	21	2	7	2		3			2		6		11
Morphine	54	All types	29	7	9	9		1	2	2	1	10	1	2	19
Nu 1196 10-20 mg.	52m 53b	All types	30	11	6	6		1			2	1	5	2	11
Nu 1196 30 mg.	67m 69b	All types	47	7	7	7		1	3	1	4	3	1	1	14

m = mothers

b = babies

\*Excluding one stillborn anencephalic monster.

In Table II indicating fetal depression, patients are grouped according to the type of anesthesia used for delivery. However, with certain drugs, all the mothers were delivered under inhalation anesthesia and had to be compared with similar groups.

Among the seven patients who received Methadon and were delivered under regional anesthesia, five babies cried within the first 15 seconds, but two were secondarily depressed and required more than one minute of stimulation to initiate good crying.

As indicated earlier, this drug was discontinued because respiratory depression increased greatly as dosage was augmented.

Of the eighteen patients given morphine and delivered under regional anesthesia, ten, or 56 per cent, of the babies cried within the first 15 seconds; three, or 17 per cent, were depressed and required more than one minute of stimulation.

Of the fourteen patients given Nu 1196 in 20 mg. or smaller doses who delivered under regional anesthesia, eleven, or 79 per cent, of the babies cried within the first 15 seconds, and two, or 14 per cent, were depressed, i.e., required more than one minute of stimulation to initiate good crying and breathing. Of the thirty-eight babies of patients who received 30 mg. of Nu 1196 and delivered under regional anesthesia, twenty-five, or 66 per cent, cried within the first 15 seconds, and six, or 16 per cent, required more than one minute of stimulation to initiate good crying and breathing.

Adding scopolamine to Nu 1196 appeared to increase the tendency to apnea in the babies of the twelve patients delivered under regional anesthesia. Only six of the babies cried within the first 15 seconds and two showed some degree of respiratory depression.

In patients receiving Nu 1196 orally and subcutaneously, there were no cases delivered under regional anesthesia alone, but fifteen were delivered under inhalation anesthesia and four of the babies were depressed. Among the nine women delivered with regional-inhalation combination three babies were depressed. Whether this depression was due to the anesthetic or the longer action of the analgesic drug given orally is not known.

In thirty-two patients who received morphine and scopolamine and delivered under inhalation anesthesia, sixteen of the babies cried within the first 15 seconds; fourteen were depressed and required more than one minute of stimulation to initiate good breathing and crying.

In twenty-three patients who received morphine alone and delivered under inhalation anesthesia, thirteen of the babies cried within the first 15 seconds; eleven of the babies were depressed.

Twenty patients received morphine and Prostigmine and delivered under gas anesthesia. In this group seventeen of the babies cried within the first 15 seconds while 5 were depressed.

These results are summarized in Table III.

In some of the groups delivered under regional anesthesia an attempt was made to correlate the fetal depression with time of administration of the drug. The results are shown in Table IV.

In those cases marked with an asterisk on the chart there were other significant factors, e.g., one baby delivered by breech extraction and the other by difficult low forceps, which more likely caused the depression than the drug administered. With Methadon the depressions occurred when the drug was administered 3 to 4 hours before delivery. With morphine, the depression appeared to occur during the 31 to 240 minute period after administration. Nu

1196 in doses of 20 mg. or less caused no significant depression. With Nu 1196 in 30 mg. doses, the depression appeared to occur in the 31 to 120 minute period after administration with the largest number in the 31 to 60 minute period.

TABLE III

DRUG	TYPE ANESTHESIA	NO. CASES	SPONTANEOUS BREATHING	
			1-15 SECONDS	DEPRESSED
Nu 1196 10-20 mg.	Regional	14	11	2
Nu 1196 30 mg.	Regional	38	25	6
Nu 1196 and scopolamine	Regional	12	6	4
Methadon	Regional	7	5	2
Morphine	Regional	18	10	3
Morphine and scopolamine	Inhalation	32 Mothers 33 Babies	16	14
Morphine	Inhalation	23	13	11
Morphine and Prostigmine	Inhalation	20	17	5
Nu 1196 and scopolamine	Inhalation	21	10	10
Nu 1196 and scopolamine	Inhalation and regional	10	5	3
Summary of Methadon	All types	32	21	11
Summary of morphine	All types	54	29	19
Summary Nu 1196 10-20 mg.	All types	52	30	11
Summary Nu 1196 30 mg.	All types	67 Mothers 69 Babies	47	14

TABLE IV

DRUG		NO. CASES	TIME INTERVAL BEFORE DELIVERY (MINUTES)					
			0-30	31-60	61-120	121-180	181-240	240 PLUS
Methadon	Mothers	7	0	0	3	0	3	1
	Depressed Babies						2	1
Morphine	Mothers	18	1	4	5	6	1	1
	Depressed Babies		0	2	1			
Nu 1196 10-20 mg.	Mothers	14	1	1	4	4	3	1
	Depressed Babies				1*			1*
Nu 1196 30 mg.	Mothers	37	0	15	14	5	1	2
	Depressed Babies		0	4	2			

\*Significant factors discussed above.

Average lengths of labor did not appear to be influenced by any of the drugs used. The incidence of operative deliveries increased with the use of regional block anesthesia and was comparable in each series of analgesic drugs used.

Except for the neonatal mortality among definitely premature babies and monsters, there was one death possibly attributable to the analgesic agent. This occurred in a baby whose mother received morphine. The baby was of good size,

began to breathe and cry immediately after birth and appeared to be in excellent condition when transferred to the nursery. Twelve hours after birth it was found dead. Autopsy findings showed aspiration and acute asphyxia.

### Summary

1. Nu 1196 (Nisentil) was given subcutaneously in 30 mg. or smaller doses to one hundred eighty-six patients. It compared favorably in analgesia with any of the other drugs employed. Greater flexibility in repeated administration of the drug was possible because of its short action.

2. Administered orally, Nu 1196 (Nisentil) did not seem to prolong or enhance the degree of analgesia. Its effect was not as great as when given parenterally. Nu 1196 with scopolamine was given to forty-three mothers. Fetal depression in this group was greater than when the drug was used alone.

3. Nu 1196 (Nisentil) appeared to have a moderate hypnotic effect on the mothers and produced somewhat less fetal depression than any of the other drugs used. Depression seemed most likely to occur in the 31 to 120 minute period after administration. There were no ante- or neonatal deaths attributable to the drug.

4. Morphine used alone in the amounts stated gave less analgesia than Nu 1196. There was no appreciable difference in analgesia when Prostigmine was added to morphine.

5. Methadon in larger doses gave nearly the same degree of analgesia as Nu 1196 but when given in larger doses there was marked fetal depression. Its use was therefore discontinued.

6. Side effects were minimal with all drugs. Nausea and emesis were most prominent. A few patients receiving Methadon complained of tingling at the area of injection.

7. There was no increase in the incidence of operative deliveries attributable to Nu 1196.

The authors desire to express their grateful appreciation of the helpful suggestions and criticisms given this project by Dr. E. G. Gross of the Department of Pharmacology and Dr. S. C. Cullen of the Division of Anesthesiology of the Department of Surgery.

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## DIFFUSE ADENOSIS: A RARE INVASIVE LESION OF THE UTERUS

HEINRICH W. NEIDHARDT, M.D., AND JAMES T. DOWNS, III, M.D.,  
GALVESTON, TEXAS

(From the Departments of Pathology, and of Obstetrics and Gynecology, University of Texas Medical Branch)

THE purpose of this paper is to present a condition, the nature of which has not been satisfactorily explained in terms of any of the familiar processes known to occur in the cervix and uterus. The authors have been unable to find a reference in the literature to any condition similar to that which is about to be described.

The term "diffuse adenosis" was chosen to describe a unique process affecting the entire uterus, cervix, and parametrium, and characterized by the presence of innumerable mucus-secreting glands in the affected tissues. In the selection of this term there is no intended implication as to the exact nature of the condition; however, the resemblance of the infiltrations to true cervical glands is apparent. In view of the course of the case under consideration, it would seem likely that this condition had its origin in the cervical glands, since the disease had apparently been present in the cervix for several months. This observation would immediately raise the question of a malignancy arising in the cervical glands.

The probability of this condition representing a form of invasive carcinoma certainly cannot be denied since the evidence of invasion is unequivocal, although the cytological evidences of malignancy are not striking. In any case, carcinoma of this type has not been encountered in the authors' experience.

It has been stated by Te Linde in the chapter on endometriosis in his textbook, *Operative Gynecology* that excessive growth and invasiveness without malignant characteristics are limited in the human being to the glandular and stromal elements of the endometrium. If the condition under discussion could be considered nonmalignant, a comparison to adenomyosis might be justified.

A condition of the sort described above occurred in a 44-year-old woman who was first seen on the Gynecology Service in May, 1947, at which time she complained of excessive vaginal bleeding with pain in the left side and back. The previous menstrual history was that of regular periods occurring every twenty-eight to thirty-one days, lasting eight days. She had had thirteen living children and three abortions. The physical examination revealed a chronically ill woman, about 45 years of age, who showed slight elevation of the blood pressure, a temperature of 99.4° F., and a pulse rate of 80. The uterus was enlarged to twice its normal size and was freely movable. The cervix was greatly enlarged and bled freely on manipula-

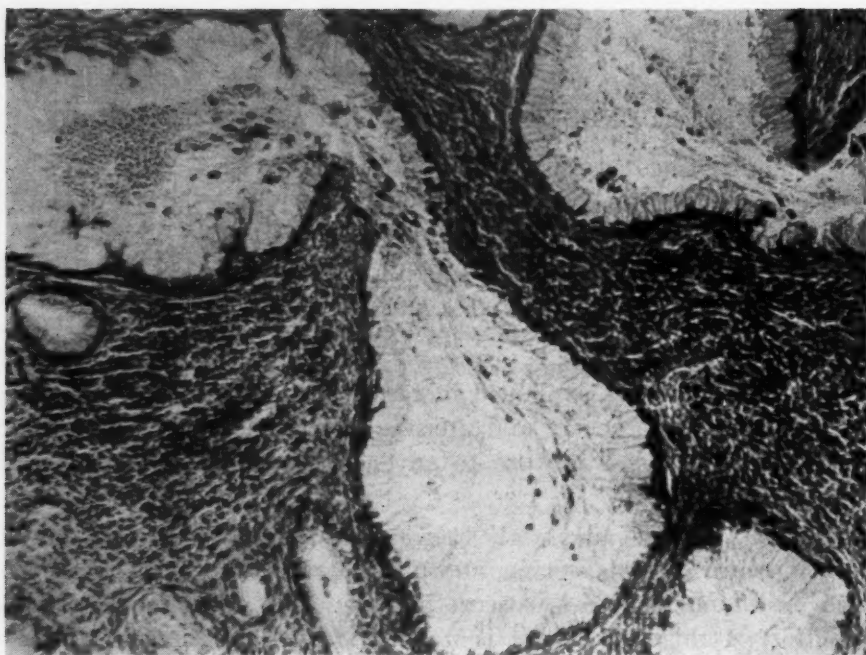


Fig. 1.—Cervical biopsy, May 12, 1947. Note the profusion of functioning cervical glands and the inflammatory reaction.

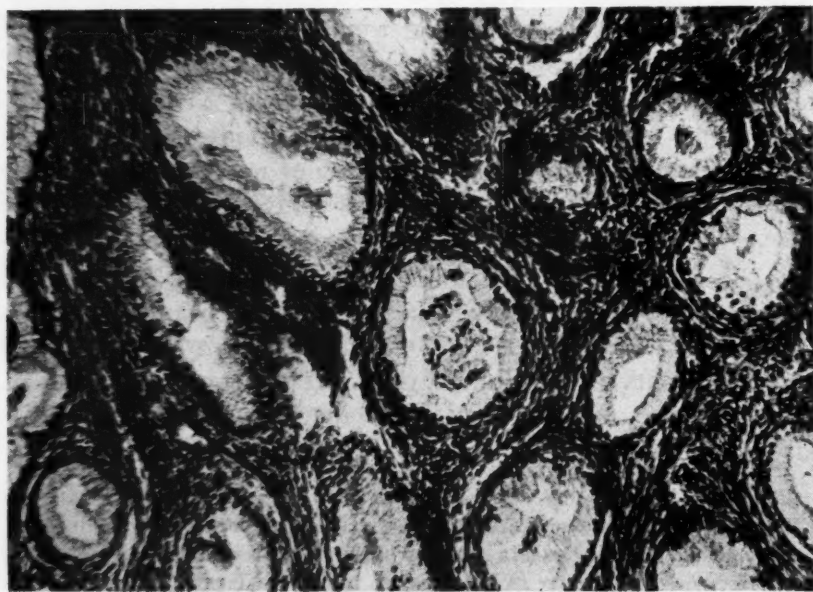


Fig. 2.—Operative specimen (cervix). Note similarity in appearance to Fig. 1.

tion. The laboratory examination was negative except for a red blood count of 3.3 million with 10.1 Gm. of hemoglobin and 10,700 white blood cells.

A dilatation and curettage, performed a few days after admission to the hospital, resulted in a pathological diagnosis of acute and chronic cystic cervicitis, the endometrial scrapings apparently being indistinguishable histologically from the cervical biopsy.

During the months of June and July the patient was readmitted and treated on three different occasions and at each time cervical biopsies revealed an acute and chronic cervicitis with numerous mucus-secreting glands present in the cervical fragments.



Fig. 3.—Operative specimen. Endometrium showing both typical proliferative endometrial glands and the aberrant mucus-type glands. Compare with Fig. 2.

On November 3 the patient was readmitted for the fourth time with the same complaints. During this admission a bilateral salpingo-oophorectomy and total hysterectomy were performed. At operation there appeared to be a chronic indurative process involving the anterior uterine wall, and the bladder floor, the parametrium, and the vaginal cuff. In the parametrium, especially between the uterus and bladder, and extending to each wall of the pelvis, yellowish plaques were noted which exuded a gelatinous material on section. Post-operative recovery was uneventful and the patient was dismissed on November 18.

Complete description of organs and tissues removed was as follows:

*Gross Description.*—The specimen consisted of a uterus including the cervix, both tubes, and ovaries (Fig. 7). The uterus including cervix measured 110 by 90 by 50 mm. The cervical os was patent. The surface was pinkish gray in color with a granular appearance. The endometrial cavity contained a large blood clot. The endometrium measured about 1 mm. in thickness. The myometrium showed asymmetrical thickening measuring from 22 to 30 mm. in thickness. The cut surface of the myometrium had a whorled fibrous appearance and there were numerous irregular cleftlike spaces seen, varying in size from 1 to 6 mm. in greatest dimension. Most of these contained gelatinous material and a few contained a small amount of blood.

The cleftlike spaces were present in the myometrium and fundus, the lower uterine segment, and the stroma of the cervix. Both tubes showed subserosal hemorrhages. The right tube measured approximately 110 mm. in length and 5 mm. in diameter in the proximal portion and 43 mm. in the distal portion. The left tube showed similar characteristics. They sectioned with moderate ease, showing some thickening of the wall. The ovaries averaged 30 mm. in greatest dimension and sectioned with moderate ease displaying hemorrhagic follicles and a corpus luteum.

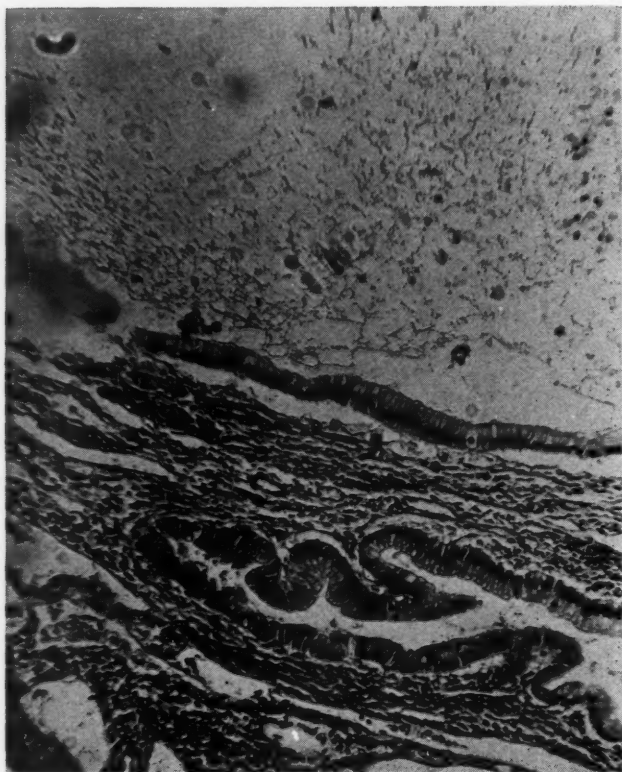


Fig. 4.

Fig. 4.—Operative specimen. Myometrium showing cystic space lined by mucus-type cylindrical epithelium. These were encountered throughout the myometrium. (See Fig. 7.)



Fig. 5.

Fig. 5.—Operative specimen. Parametrium. Note presence of glandular elements and fat cells in upper left.

**Microscopic Findings.**—Section through the cervix showed rather marked coagulation necrosis of the covering epithelium, much of which was desquamated. The fibromuscular stroma was diffusely infiltrated with innumerable regular-appearing cervical glands showing marked secretory activity. The nuclei were small and uniform appearing. The glands had essentially the same appearance in all portions of the section. The remainder of the stroma was infiltrated with round cells. Section through the uterus showed a moderately atrophic endometrium and typical glands which showed no evidence of secretory activity. The stroma showed considerable tendency to fibrous metaplasia. Other sections showed in addition to the usual endometrial glands, atypical slightly irregular glands showing much secretory activity. The cytoplasm of the cells contained secretory vacuoles and the glands bore a resemblance to ordinary cervical glands. The myometrium also showed diffuse scatterings of similar mucus-secreting glands still bearing a striking resemblance to cervical glands. Most of the



glands were lined with regular cells showing no nuclear changes. A few areas showed pleomorphic cells and there were very rare mitotic figures. In no case, however, was nuclear stratification observed. Some of the myometrium showed the glands to be widely dilated and cystic, containing large amounts of mucoid material and showing atrophy and desquamation of the lining epithelium. Section through the parametrium showed a few glands within the fibrous tissue. These glands had the typical appearance of cervical glands and showed the usual cytological abnormalities. In many of the glands throughout the uterus, the secreting portions of the cells were extremely tall and had the appearance of goblet cells. Section through the ovary showed a few corpora fibrosa and thickening of the arterial walls. Section through the uterine tube showed some fusion of the mucosal folds and thickening of the wall. There were occasional foci of round cell infiltration.

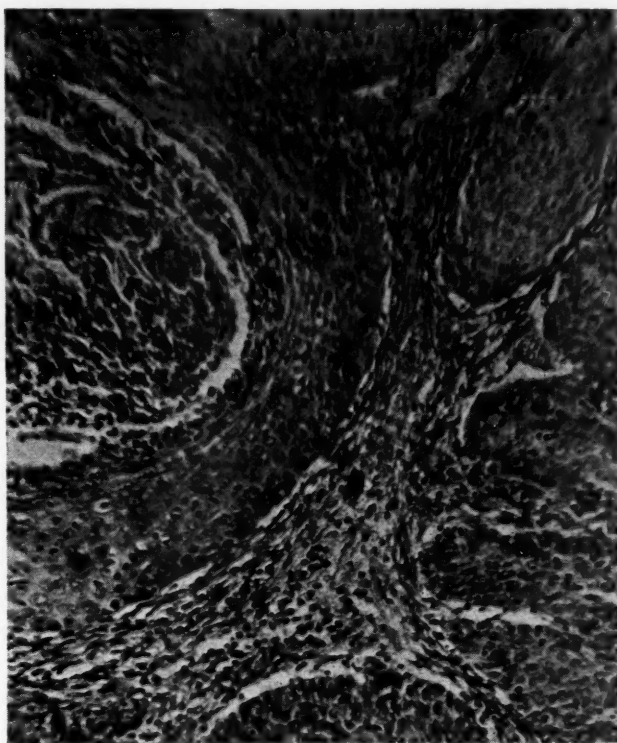


Fig. 6.—Biopsy of vaginal vault, June 18, 1948. Epidermoid carcinoma.

*Pathologic Diagnosis.*—(1) The lesion probably represents an atypical low-grade mucoid type of adenocarcinoma. Note: the cytologic characteristics of a malignant lesion are largely lacking. However, there is definite invasion. The origin of the lesion is quite obscure. (2) Chronic salpingitis.

The patient returned again on February 6 by request of the follow-up service, at which time she was complaining of painful urination. A mass was noted at the apex of the vagina and involving the floor of the bladder. The vaginal walls appeared well healed. Cystoscopic examination showed some frondlike growths in the bladder. These were biopsied and reported as chronic cystitis.

She was next seen on June 18, again by request, at which time she had no complaints. Pelvic examination showed the same mass above the vagina and now an ulceration of the vaginal vault. This was biopsied and was reported as Grade III, squamous-cell carcinoma. At this time the patient was referred to the radiologist for roentgen therapy.



Fig. 7.—Operative specimen. See text for description.

### Discussion

In the management of this case, two points should be considered. Hysterectomy was delayed because of the very evident infection of the cervix, which was partially controlled by local measures, antibiotics, and an electrocoagulation. Perhaps irradiation therapy should have been given sooner, but the uncertain nature of the condition and the general well-being of the patient delayed this measure until there was proved malignancy.

The subsequent development of the squamous-cell carcinoma in the vaginal vault presented a complicating factor in the management of this case, and, presumably, should be regarded as independent of the adenomatous lesions. The likelihood of its origin from the vaginal mucous membrane is strengthened by the fact that other sites of origin have been ruled out.

### Summary

1. A case of an atypical invasive glandular lesion of cervix and uterus was presented.
2. Discussion of the clinical management was given.

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## THE PREVENTION OF HEADACHE AFTER SPINAL ANALGESIA FOR VAGINAL DELIVERY BY THE USE OF HYDRATION AND A 24 GAUGE NEEDLE

BARNETT A. GREENE, M.D., MORRIS GOLDSMITH, M.D., AND  
SAMUEL LICHTIG, M.D., BROOKLYN, N. Y.

*(From the Brooklyn Women's Hospital)*

THE postspinal headache is a serious objection to the use of spinal analgesia in obstetrics. Before we devoted extra attention to avoiding it, our obstetricians were reluctant to have their patients receive spinal analgesia.

### Incidence

The incidence of this complication in several reports of spinal anesthesia for vaginal delivery has varied from 20 per cent<sup>1</sup> to zero.<sup>2</sup> Most observers find it too frequent to be disregarded. These apparently conflicting experiences are confusing unless the problem of postspinal headache is understood as depending on a large number of subtle factors which may influence the observed incidence of headache.

The apparently greater importance of the postspinal headache problem in our service is attributable to the following factors:

- a. The majority of our patients are up and out of bed on the first or second postpartum day.
- b. Ours are largely private cases and the patients do not hesitate to voice their complaints.
- c. The patients are chiefly of the Mediterranean and Semitic peoples whose threshold for the perception or complaint of pain is lower than that of the Negro, Asiatic, and Scandinavian groups.
- d. Postspinal headaches in our patients are carefully sought and reported. The complaint, however, is never solicited of the patient.

These factors are variables which prevent comparison with any series of cases reported by others, even when the technique of spinal anesthesia has been identical. We have, therefore, controlled our results by our own earlier experience with the same group of obstetricians and the same types of patients.

### Pathogenesis

We began this study in February, 1947. Out of many diverse and conflicting statements in more than one hundred articles, we formulated the following as a working basis. The common type of postspinal headache is due to leakage of spinal fluid through the persisting opening in the dura with the consequent development of a subnormal volume and pressure of cerebrospinal fluid. This, in turn, leads to dilatation of intracranial veins and, in the upright position, to traction on the anchoring structures of the brain, the stimuli directly causative of headache. The subnormal volume of spinal fluid results

from a situation in which the rate of loss through the dural puncture is greater than the rate of restoration by the choroid plexus. The rate of leakage depends chiefly on the size of the puncture and the time at which the patient assumes the upright position. The rate of re-formation of spinal fluid is dependent on the tonicity and volume of water in the blood and interstitial spaces. Water which is free to influence the formation and absorption of cerebrospinal fluid (which we term "free water" for convenience) is water that is in excess of the prior demands for water made by the more vital functions of temperature regulation, maintenance of blood volume, urine formation, and pulmonary respiration. Water that is hypotonic is more effective in increasing the volume of cerebrospinal fluid. A large percentage of postpartum patients do not have a volume of hypotonic water available in sufficient quantity to maintain the new formation of cerebrospinal fluid at a rate which can compensate for a relatively large loss by leakage. "Free water" is probably markedly reduced in these patients by the less than normal intake of fluid and food during labor and the first few days of the puerperium coupled with the larger than normal losses of water during the same period. The fluid output is larger than normal because of the increased elimination of water with sodium salts that results from the hormonal changes of the puerperium and because of the considerable blood loss during the third stage of labor and the postpartum flow of lochia rubra.

### Methods

These facts have justified the trial of two possible means of reducing the incidence of postspinal headache:

1. To decrease the rate of loss of cerebrospinal fluid by minimizing the size of the lumbar puncture wound.
2. To increase the rate of formation of cerebrospinal fluid by enlarging the volume of "free water" in the postpartum patient.

1. The size of the dural opening may be decreased by attention to several details regarding the needle and the technique of lumbar puncture but the primary factor is the diameter of the spinal needle. We therefore tried a 24 gauge spinal needle. Lumbar puncture with a 24 gauge spinal needle requires the aid of a double needle\* system (a needle within a needle) because of the great flexibility of the long 24 gauge needle. The principle of the double needle originated with Hoyt in 1922.<sup>3</sup> In the United States there has been no double needle commercially available since the Hoyt needle was discontinued for lack of general acceptance.<sup>4</sup> The outer needle is a 20 gauge, 7.5 cm. spinal needle. The inner needle is 24 gauge, 10 cm. which accurately fits the outer needle. Each of the two needles have their own stylets.

The 24 gauge needle allows spinal fluid to flow so slowly that, for speed and convenience, the anesthetic drug should be in solution, e.g., Pontocaine, Metycaine, or Nupercaine. The 20 gauge needle, with its stylet in place, is introduced through the anesthetized skin wheal and subcutaneous area to the interspinous ligament or ligamentum flavum. A resistance greater than subcutaneous tissue is felt at this depth, where the point of the needle is within 1 cm. of the dura. The stylet is removed and the 24 gauge needle, with its own stylet in place, is then passed through the lumen of the 20 gauge needle into the subarachnoid space. In early trials the tendency is either to push the 20 gauge needle too far so as to puncture the dura or to stop at a point short of the ligament. If the 20 gauge needle is in correct position the puncture of the dura by the inner 24 gauge needle is easily and gently ac-

\*The double needle which we have been using is that suggested by Mr. Oscar Schwidetzky of Becton, Dickinson and Company in response to our inquiry.



complished. When the inner needle readily passes beyond the point of the outer needle, it is most probable that the former is in the subarachnoid space. The spinal fluid comes out so slowly that one should wait and watch the hub of the needle for a few seconds. If fluid does not come, the stylet of the 24 gauge needle is reinserted and the two needles are pushed on as one unit until the projecting inner needle is felt to pierce the dura.

2. The volume of "free water" is increased by encouraging water drinking during and after labor. Ten glasses of fluids are ordered for each of the first two days after delivery. When dehydration or blood loss is greater than usual, the patient receives one or more infusions during or after labor, as a rule, 1 L. of 5 to 10 per cent glucose in distilled water, administered slowly. Normal saline is less effective than distilled water with glucose. As an aid in retaining "free water" in the body, we utilize the antidiuretic property of whole posterior pituitary extract. The dosage is 10 units of posterior pituitary extract (1 c.c. of obstetrical Pituitrin) injected hypodermically every 12 hours for three doses. Posterior pituitary extract increases reabsorption of water by the renal tubular cells while allowing a disproportionately larger excretion of sodium ions.<sup>5</sup>

No breast difficulties have been observed despite the large proportion of our patients who do not nurse their infants. This is due in part probably to the prophylactic use of estrogenic drugs.

### Headache, Diagnosis and Classification

Residents and obstetricians were encouraged to cooperate in recording and reporting all headaches, although little effort was needed in this direction with most of our staff. Where an obstetrician or patient is aware of the fact that a spinal puncture has been performed, there is a tendency for either of them to attribute any headache to the lumbar tap. It is therefore necessary that the criteria of a true postspinal headache be used in the diagnosis of a headache. A headache was judged to be of spinal origin when it was aggravated by sitting up and relieved by lying down. A headache was counted even if it was complained of only once or lasted one day, in which case it was classified as "mild"; if it was present on more than one day it was considered to be "moderate"; if it prevented the patient from getting out of bed or persisted for five days it was "severe."

### Results

We have attempted to evaluate the influence of the size of the needle by the following two series:

TABLE I. PERCENTAGE OF HEADACHES

	NO. OF PATIENTS	MILD	MODERATE	SEVERE	TOTAL
22 Gauge needle without Pituitrin and water	93	8	12	6	26
24 Gauge needle without Pituitrin and water	120	0.8	0.8	0.8	2.5

These two series of vaginal deliveries were anesthetized by the same personnel; all received Nupercaine and glucose intraspinally; all were accorded routine postpartum care and observation; none received any special prophylactic measure against headache.

The incidence of 26 per cent in the 22 gauge series was reduced to 2.5 per cent in the 24 gauge series. The difference between the two series is statis-

tically significant in view of the mathematical finding that this difference is larger than three times the standard error of the difference.<sup>6</sup> This result is especially remarkable when it is realized that even a single complaint of headache on one day sufficed to bring the patient to our attention and record. Furthermore, the 24 gauge series was done by anesthetists learning to use the 24 gauge needle. We suspect that the single severe headache in the 24 gauge series was the result of an inadvertent puncture with the 20 gauge portion of the "double needle." We now test every "double needle" puncture for an accidental puncture with the 20 gauge needle by withdrawing the 24 gauge needle before removing the 20 gauge needle. A 20 gauge needle puncture is quite likely to be followed by a moderate or severe headache in our experience with postpartum patients. Seven patients were deliberately punctured with a 20 gauge needle; four developed headache; two suffered to a severe degree. We were unable to continue the 20 gauge series to obtain the number of cases required for statistically significant results.

The following observations on the incidence of headache after spinal anesthesia for cesarean section confirm the importance of the gauge of spinal needle:

TABLE II. PERCENTAGE OF HEADACHES IN CESAREAN SECTION

	NO. OF PATIENTS	MILD	MODERATE	SEVERE	TOTAL
16 Gauge needle (with ureteral catheter for continuous spinal anesthesia)	26	15	0	27	42
20 Gauge needle	32	18.7	0	0	18.7
22 Gauge needle	26	3.8	3.8	0	7.7

These groups show a decrease in headache incidence with each reduction in size of needle diameter. In spite of the small number of cases, there is tested statistical significance in the difference between the 16 gauge and the 22 gauge series. Especially noteworthy is the comparative incidence of headaches of severe degree.

We have tried to determine the value of hydration by the following two series:

TABLE III. PERCENTAGE OF HEADACHES IN VAGINAL DELIVERIES

	NO. OF PATIENTS	MILD	MARKED	SEVERE	TOTAL
22 Gauge needle without Pituitrin and water	93	8	12	6	26
22 Gauge needle with Pituitrin and water	108	6.5	2.8	0.9	10

These two series differed only with respect to the special effort to increase hydration in one group by the use of Pituitrin and encouraged drinking of water. Patients were not informed of the reason for these orders.

The incidence of 26 per cent in the 22 gauge series without hydration was decreased to 10 per cent in the 22 gauge series with hydration, a difference of verified statistical significance.<sup>6</sup> Of equal importance is the fact that the headaches in the latter group were largely of the mild variety. Further evidence of the value of forced hydration, although not conclusive in itself, is our experience with three cases accidentally punctured with the 20 gauge outer needle in our early trial of the double needle system. These three cases were given Pituitrin and water to prevent the expected headache. One headache occurred and that one was very mild, a single complaint for only one day.

The relative efficacy of reducing the needle size as compared with increasing hydration is clear. The 24 gauge needle produced a far greater improvement over the 22 gauge control series than did the use of Pituitrin and increased drinking of water.

The use of Pituitrin alone, without the forcing of fluids, was not tested because Zappala<sup>7</sup> and others had found it valueless. In four cases in which Pituitrin was given but water had been inadvertently not encouraged headache occurred in every instance. This experience is not significant; nevertheless, it discourages any idea of a specific value of Pituitrin alone in the formation of cerebrospinal fluid, as was once believed.

Another relevant observation concerning the value of hydration is the finding in five cases that headache was prolonged and severe whenever the obstetrician ordered any dehydration therapy, e.g., oral magnesium sulfate, for relief of a postspinal headache. Such measures, once highly recommended for the treatment of headache due to leakage of spinal fluid, are definitely contraindicated. The aggravation of postspinal headache by dehydration is to be expected in view of the experimental evidence that oral magnesium sulfate lowers spinal fluid pressure<sup>8</sup> and that dehydration increases the frequency and severity of headache experimentally induced by drainage of spinal fluid.<sup>9</sup>

### Discussion

The importance of the size of the dural opening has been stressed in the literature for many years. Yet this essential feature in the best-supported theory of the pathogenesis of common variety of postspinal headache still is not accepted universally. Raney and Raney<sup>10</sup> reject the leakage theory and favor an explanation depending on cervical spinal trauma during positioning for the spinal puncture. Adler<sup>11</sup> stresses the psychogenic causation. Weintraub, Antine and Raphael,<sup>12</sup> who have employed the 22 gauge needle only to continue to meet a high incidence of headache, have lost faith in the leakage theory and have sought some other explanation such as orthostatic hypotension following evacuation of an abdomen distended by a full-term fetus. Compressive abdominal dressings have been tried before<sup>13</sup> with some success but are destined to be of incomplete benefit as long as the fundamental factors of leakage and inadequate re-formation of cerebrospinal fluid are not properly understood. A low cerebrospinal fluid pressure may be temporarily raised by a rise in intra-abdominal pressure. Without reducing leakage or increasing cerebrospinal fluid formation, the prevention of postspinal headache is on an uncertain basis.

The fact which has disturbed many anesthetists who have tried to prevent postspinal headache with the use of a 22 gauge needle is that the complaint has continued to appear in significant incidence despite the use of so fine a needle. The absence of a commercially available 24 gauge needle in this country and the general unawareness of the practicability of a 24 gauge needle have encouraged the belief that the limit of prevention of leakage had been reached. Our experience confirms anew the value and practicability of reducing the size of a dural puncture to that created by a 24 gauge needle.

The fact that headache still appeared in 2.6 per cent of cases punctured with a 24 gauge needle indicates that, if we are to eliminate postspinal headache completely, attention must be directed toward other factors in its pathogenesis. It has long been known that the problem of postspinal headache is complicated by variables other than the size of the dural puncture. The existence of these other determinants of a postspinal headache is suggested by the fact that lumbar puncture even with a 16 gauge needle is not always



followed by a headache. A patient punctured with a 16 gauge needle may be less likely to suffer a headache than one punctured with a 20 gauge needle contrary to expectation according to the leakage theory, if the former is favored by secondary factors which influence the complaint of postspinal headache. These secondary factors are:

- a. The duration of horizontal position after puncture;
- b. the threshold for pain and readiness to complain;
- c. the presence of stimuli which distract attention from headache;
- d. the coincidental use of analgesics for wound pain, and, finally, but most important,
- e. the state of hydration.

The value of administering parenteral fluids has been repeatedly reported.<sup>13-16</sup> The relationship between the state of hydration and the susceptibility to postspinal headache, however, has been emphasized only by Masserman.<sup>9</sup> The varying degrees of hydration among apparently normally hydrated patients seem to us to be an essential but overlooked factor in the seemingly unpredictable incidence of a postspinal headache. Solomon<sup>14</sup> measured lumbar spinal fluid pressure at varying intervals after lumbar puncture in a series of psychiatric patients. Many showed a persistently subnormal pressure; others, however, rapidly and spontaneously restored the pressure to normal. Cushing<sup>17</sup> established the fact that the drinking of water influences the hydration of the cerebrospinal canal. Weed<sup>18</sup> and Kubie<sup>19</sup> demonstrated the close relationship between intravenous hypotonic fluid and cerebrospinal fluid volume. We noted the apparently small volume and low pressure of spinal fluid in many dehydrated surgical patients. Alpers<sup>16</sup> observed that the patients who were susceptible to a postspinal headache developed an unusually low spinal-fluid pressure at the end of withdrawal of 25 c.c. spinal fluid, indicating that they had a low initial volume and a slow rate of re-formation of spinal fluid. All of these points led us to believe that we might decrease the incidence and severity of the headache by increasing body hydration prophylactically. By insuring a positive water balance, especially with water not bound by sodium ions, we might increase the rate of restoration of cerebrospinal fluid volume and pressure so as to offset the loss by dural leakage.

The reported value of posterior pituitary extract in the prevention and treatment of postspinal headache<sup>13, 14, 16</sup> is best explained by its known property of increasing the hydration of the cerebrospinal axis, as shown by its use in the clinical reproduction of epileptiform seizures.<sup>20</sup> There has not been any convincing evidence published to indicate any specific secretory effect of Pituitrin on cerebrospinal fluid. It has been established, however, that posterior pituitary extract is antidiuretic while allowing a disproportionate excretion of sodium ions in the urine. We have therefore employed Pituitrin as an auxiliary means of insuring hydration in the event the patient fails to follow the order to drink ten glasses of fluid a day during the first two days post partum.

The validity of this reasoning has been confirmed by the results obtained by comparing the two series of cases done with the 22 gauge needle. Improved hydration, produced by encouraged drinking of water and three doses of Pituitrin, reduced the probability of a headache from 1 in 4 to 1 in 10. Supportive evidence is afforded by the prophylactic effect of large infusions in preventing headache in every one of the few cases in which such restorative therapy was indicated by clinically evident dehydration or blood loss.

The factor of adequate hydration is very helpful in understanding the following observations:



1. The incidence of postspinal headache after vaginal delivery is greater (26 per cent) than after cesarean section (8 per cent) despite the use of 22 gauge spinal needles in both types of delivery.<sup>21</sup> This fact has also been reported by Weintraub, Antine, and Raphael.<sup>12</sup> While the presence of wound pain, the postoperative use of morphine and less early ambulation may be part of the explanation, the most likely cause for the decreased incidence of headache after cesarean section is the greater attention to adequate hydration of the cesarean patient, especially with infusion and transfusion.

2. The incidence of postspinal headache after vaginal delivery is greater than after the usual abdominal operations. For example, no headache occurred in our series of 100 consecutive herniorrhaphies performed with spinal anesthesia administered through a 22 gauge needle.<sup>21</sup> Here, too, a valuable prophylactic measure is the more adequate hydration of the surgical patient. The postpartum patient, as a rule, loses more blood and is more dehydrated than one who has undergone an elective hysterectomy or cholecystectomy. Yet the latter type of patient is usually given one or more infusions while the postpartum patient is rarely infused because blood loss of 100 to 250 c.c. during the third stage of labor is normally expected and the further loss of water and blood is so gradual during the flow of the lochia rubra. The majority of patients are more anemic on the fifth day post partum than most postoperative patients.<sup>21</sup>

3. All three of the cases that developed headache in the 24 gauge series suffered blood loss sufficient to lower their hemoglobin determinations on the fifth day post partum to 53, 56, and 58 per cent (Sahli), respectively. The loss in each instance was gradual and therefore no infusion or replacement therapy seemed necessary. Indeed, patients who suffered unusual degrees of dehydration or blood loss seemed especially prone to the development of postspinal headache in the absence of adequate fluid restoration. On the other hand, the patients who received infusions early for any reasons did not have headache, regardless of the size of the needle or the omission of Pituitrin.

The use of increased hydration is especially indicated in preventing or mitigating headache when a lumbar puncture is unavoidably performed with a needle larger in diameter than a 24. The efficacy of hydration, however, is limited. If needles 16 to 20 gauge are used, hydration, unless vigorously enforced, is not likely to be able to restore spinal fluid as quickly as it is lost through the large dural opening. An evidence of this is the finding of 42 per cent headaches in the 16 gauge series of cesarean sections despite routine postoperative infusion with one to two liters of fluid. The finer the needle the less fluid is needed to prevent headache. Even with a 24 gauge needle, however, special attention should be given to improving the hydration of postpartum patients. Too little notice has been taken of the fact that the average obstetrical patient is significantly dehydrated and anemic during the first postpartum week.

Early in this report we discussed the reasons for the high incidence of postspinal headache (26 per cent) when our patients have been punctured with a 22 gauge needle and received routine postpartum care. This incidence is larger than that reported by any other authors. In spite of the fact that the conditions which might influence our results unfavorably have remained the same, our results with the 22 gauge needle and increased hydration or with the 24 gauge needle without hydration are better than the average incidence published by others who have specially studied this subject.

The value of the 24 gauge needle and increased postpartum hydration has been tested by using each measure separately. It is apparent, however,

that each does not exclude the use of the other. In fact, it is our current practice to use both so as to try for a record even better than the 2.5 per cent noted in the 24 gauge series of cases without increased hydration.

### Summary

1. We have employed the "leakage theory" of the pathogenesis of postspinal headache which may be stated as follows:

- a. Postpuncture leakage permits a fall in cerebrospinal fluid volume and pressure which, in turn, causes dilatation and traction of anchoring, vascular cerebral structures. If this pain-producing process exceeds the pain threshold of the patient, the result is a typical postspinal headache.
- b. Postpuncture leakage is proportionate to the diameter of the spinal puncture needle.
- c. The restoration of cerebrospinal fluid is related to the state of hydration and is decreased by the presence of other demands which compete for body water.
- d. The upright position increases the rate of leakage and aggravates the changes in the cerebral attachments and veins.

2. Postpartum patients, as a group, are more susceptible to the appearance of postspinal headache than any other class of patient for spinal anesthesia because they tend to be more dehydrated, they are more quickly ambulatory, and their pain threshold is lower.

3. The development, rationale, and technique of using a 24 gauge spinal needle are described.

4. The importance of hydration, aided by the antidiuretic factor in Pituitrin, is discussed with relation to its place in the theory of pathogenesis of postspinal headache.

5. The incidence of headache after spinal analgesia for vaginal delivery was studied under controlled conditions to evaluate two important factors, i.e., the diameter of the lumbar puncture needle and the degree of postpartum hydration.

6. A control series of 93 unselected patients who were punctured with a 22 gauge needle and received no increased hydration showed a headache incidence of 26 per cent.

7. Another series of 120 unselected patients who received no increased hydration but were punctured with a 24 gauge needle had a headache incidence of 2.5 per cent, a statistically significant reduction from the control series.

8. A third series of 108 unselected patients who were punctured with a 22 gauge needle but received increased hydration showed a statistically significant reduction of headache incidence to 10 per cent.

### Conclusions

This controlled study of three series of spinal analgesia cases for vaginal delivery demonstrates the exceptional value of using the 24 gauge spinal needle and the principles of hydration to achieve a significant reduction in the incidence and severity of postspinal headache.

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## OVARIAN NEOPLASMS IN CHILDREN

GEORGE SCHAEFER, M.D., FOREST HILLS, N. Y., AND EDWARD C. VEPROVSKY,  
M.D., F.A.C.S., FLUSHING, N. Y.

*(From the Department of Obstetrics and Gynecology, Queens General Hospital and the  
New York Medical College)*

OVARIAN neoplasms in children differ from those in adults in several respects: they are more rare in children, they are more frequently incorrectly diagnosed, and they are more commonly associated with complications.

The relative infrequency of ovarian neoplasms in children compared to adults is stressed by Abt<sup>1</sup> who quotes Olshausen as finding only sixty-one ovarian tumors in children under 10 years out of a total of 1,513 ovarian tumors he collected. Witzberger and Agerty<sup>2</sup> found only 186 cases in children under 10 years reported up to 1937. Reviewing 150 granulosa-cell tumors and 66 Brenner tumors in 1935, Bland and Goldstein<sup>3</sup> report eight granulosa-cell tumors and no Brenner tumors in children under the age of 10 years. Lull<sup>4</sup> states that sixteen cases of ovarian tumors showing signs of precocious puberty have been reported up to 1946. Barzilai<sup>5</sup> believes that one-third of 200 cases of dysgerminoma reported have occurred in children and in Novak's series of seventeen cases of dysgerminoma, four were under 15 years of age.<sup>6</sup>

Benjamin<sup>7</sup> states that the first case of ovarian cyst with torsion was reported by Carl Rokitansky in 1842 and one hundred years later Fowlie<sup>8</sup> was able to collect 125 cases of twisted ovarian cysts in children.

The majority of ovarian neoplasms in children, except those producing precocious puberty, are incorrectly diagnosed preoperatively, if a diagnosis is made at all. Since for some unknown reason torsion of ovarian tumors is more common on the right side (twelve of fifteen cases in Sneierson's and Schlesinger's<sup>9</sup> series), the most common mistaken diagnosis is appendicitis; other incorrect diagnoses which have been made are intussusception, mesenteric adenitis, Meckel's diverticulum with obstruction, and pyelitis.

This report includes six cases of ovarian neoplasms operated on in children in a twelve-year period from January, 1936, to December, 1947, at the Queens General Hospital. During this period there were 234 ovarian neoplasms operated upon from a total of 10,413 gynecological admissions. A brief summary of each of the six cases follows.

CASE 1.—M. L., No. 75025, a 7-month-old white child was admitted to the Queens General Hospital on Aug. 20, 1938, because of slight fever and irritability. Her mother stated that following an upper respiratory infection four days ago, the child had continued to cry and draw her legs up on her abdomen frequently. There had been no vomiting and no change in her bowel habits. The past history was not contributory. Examination revealed a temperature of 101.4° F.; there was moderate rigidity on the right side of the abdomen and pressure over this area caused the child to draw her legs up on her abdomen. No mass was felt on rectal examination. The white blood count was 14,800 cells per c.mm. with 84 per cent polymorphonuclear leucocytes. A diagnosis of intussusception was made and the child was operated upon under open drop ether anesthesia.



At operation a cyst of the right ovary measuring 6 cm. in diameter was found. A gangrenous area was present on the external surface of the cyst the pedicle of which was twisted and necrotic. The left ovary and the uterus were normal. A right oophorectomy was performed and the abdomen closed in layers without drainage. The child made an uneventful recovery and was discharged from the hospital on Sept. 4, 1938.

*Pathologic Report.*—The specimen consisted of a cystic mass measuring 6.5 cm. in diameter and containing 60 c.c. of dark brown fluid. The wall of the cyst was brown and was thickened at one point where it presents a roughened area. The interior of the cyst wall was smooth except at one area which was thick and covered with a red, friable membrane. Another area presented white calcified tissue.

*Microscopic Examination.*—Section showed some ovarian stromal tissue with massive hemorrhage and an irregular pattern of calcification. The calcified zones varied in size and distribution; some were rounded with psammoma-like bodies, others showed linear calcific areas. An eosinophilic matrix suggested early osseous formation. *Diagnosis:* Cyst with massive hemorrhage and calcification. (This may be an old dermoid although no identifiable tissue can be found in the sections studied.)

*Comment.*—The symptoms in this case were caused by torsion of the cyst pedicle which produced infarction and necrosis of the cyst wall. This child was irritable, had abdominal pain and rigidity, fever and slight leucocytosis. It was not possible to palpate a mass on recto-abdominal examination because of the rigidity of the abdominal wall. Had torsion not occurred in this cyst, it would probably have gone unrecognized for some time. On reviewing the microscopic sections of the cyst only those sections through the calcified area were found, so that no other tissue of a dermoid nature could be demonstrated.

CASE 2.—J. L., No. 97473. This 15-year-old white girl was admitted to the Queens General Hospital on Oct. 5, 1939, complaining of severe pain in the left side of her abdomen of two days' duration. For the past year the pain in her left side had been continuous with frequent exacerbations of a more acute, sharp pain which radiated to her back and down her left thigh. She had no nausea or vomiting, no urinary symptoms, and her bowel habits had been normal. She had begun to menstruate at the age of 13 years, her menses occurring every twenty-eight days and lasting four days. Except for the last two menses which occurred twenty-one days apart, her menstrual history was normal. On examination, her temperature was 99.8° F. and positive findings were limited to abdominal and pelvic examinations. The abdomen was enlarged on the left side and rebound tenderness was elicited in the left lower quadrant. On vaginal examination a large, firm mass was palpated in the left adnexal region. The uterus was anterior and of normal size, shape, and consistency. The right adnexa was not palpable. White blood count was 12,000 cells per c.mm. with 68 per cent polymorphonuclear leucocytes. A diagnosis of twisted ovarian cyst was made and the patient was operated upon several hours after admittance to the hospital.

At operation a large cystic mass arising from the left ovary filled the pelvis; the pedicle was twisted two and one-half times. A left oophorectomy was performed and the abdomen closed in layers without drainage. The patient made an uneventful recovery and was discharged on Sept. 15, 1939.

*Pathologic Report.*—The specimen consisted of a large, blue, cystic mass measuring 15 cm. in diameter. It contained opaque, brown, granular material together with recognizable caseous material, hair, and mucous membrane.

*Microscopic Examination.*—Section showed an area of hyaline cartilage with some marginal gland epithelium and adjacent squamous epithelium. In this region were also present some hypertrophied smooth muscle bundles, fat tissue, and respiratory mucosa. *Diagnosis:* Hemorrhagic dermoid cyst.

*Comment.*—In this girl, too, the symptoms arising from torsion of the cyst pedicle were responsible for her seeking medical aid, although she had apparently had symptoms referable

to the cyst for at least one year previously. Her symptoms and signs were clear-cut and a correct preoperative diagnosis was made. Pathologic examination of the specimen showed a typical dermoid cyst with hemorrhage following torsion.

CASE 3.—M. A., No. 63157. This 15-year-old white girl was admitted to the Queens General Hospital on Dec. 6, 1939, complaining of pain in the lower abdomen of eighteen hours' duration. She stated that for several years she had cramplike pain in the lower abdomen occurring about every four weeks. Her past history was not remarkable and she had never menstruated. On abdominal examination there was rebound tenderness in both lower quadrants and on recto-abdominal examination a cystic, movable mass was felt on the right side. Her temperature was 99° F. and the white blood count was 7,400 cells per c.mm. with a normal differential count. A diagnosis of ovarian cyst was made and the patient was operated upon on Dec. 11, 1939.



Fig. 1.—Wall of dermoid showing squamous epithelial lining, a sebaceous gland, and some adjacent central nervous system tissue. ( $\times 250$ .)

At operation a mass about 10 cm. in diameter was found arising from the right ovary. The uterus was normal and the left ovary contained several small follicular cysts. A right oophorectomy and an appendectomy were done following which the patient made an uneventful recovery and was discharged on Dec. 24, 1939.

*Pathologic Report.*—The specimen consisted of a cyst measuring 11 by 10 by 5 cm. covered with a smooth, thin wall. On cut section it contained cheesy material and hair; at one area a hard, bony mass was found.

*Microscopic Examination.*—Section showed sebaceous glands embedded in fibrofatty tissue mindful of scalp. A layer of overlying squamous epithelium is present. In another area compact cortical bone tissue can be made out and ossifying hyaline cartilage is seen. Some areas show central nervous system tissue. *Diagnosis:* Dermoid cyst (Fig. 1).

*Comment.*—This girl's history of lower abdominal pain dated back several years. However, she had never menstruated and the recurrent cramps at monthly intervals may have been due to the engorgement and tension that occur premenstrually. There were no symptoms or signs of torsion and a correct preoperative diagnosis was made on the basis of recto-abdominal examination. The pathologic report showed the cyst to be a dermoid.

CASE 4.—R. O., No. 30519. This 15-year-old white girl was admitted to the Queens General Hospital on March 12, 1941, complaining of pain in the abdomen of twenty hours' duration. For the past six months she had pain in the right lower abdomen at irregular intervals, the pain frequently being associated with nausea but no vomiting. Her menses began at the age of 14 years, occurred every thirty days and lasted four days. Her last menstrual period was two weeks ago. Her past history was irrelevant.

On examination, her temperature was 100° F. The abdomen was not tender and no masses were palpable. Recto-abdominal examination revealed a tender mass in the right lower quadrant. The white blood count was 8,800 cells per c.mm. with a normal differential count. The diagnosis was right ovarian cyst.

On March 17, 1941, the patient was operated upon and a right ovarian cyst measuring 6 cm. in diameter was resected. The appendix was also removed. The patient made an uneventful recovery and was discharged March 21, 1941.

*Pathologic Report.*—The specimen consisted of a rounded cystic mass measuring 6 by 3.5 by 2.5 cm. It was filled with dark red blood clots. The appendix appeared normal.

*Microscopic Examination.*—Section shows a cystic space filled with blood and mucinous material. A fibrous tissue layer with a scant ovarian stroma and a thin adjacent inner corpus luteum layer constituted the wall of the cyst. *Diagnosis:* Simple luteal cyst with hemorrhage.

*Comment.*—Symptoms of right lower quadrant pain brought this girl to the hospital although her history revealed that she had been complaining of irregular lower abdominal pain and nausea for at least six months. The diagnosis in the admitting room was recurrent appendicitis, but after the patient had been observed for several days and a normal temperature and white blood count were noted in addition to the presence of a mass on recto-abdominal examination, a diagnosis of ovarian cyst was made. The pathologic report showed this to be a simple luteal cyst with hemorrhage. Her symptoms were probably of the nature of "Mittelschmerzen" due to rupture of Graafian follicles. Bleeding had occurred into the lumen of the cyst.

CASE 5.—H. F., No. 34002. This 15-year-old white girl was admitted to the Queens General Hospital on May 4, 1941, complaining of abdominal swelling of two years' duration. Two years ago she had noted a slight swelling of the abdomen which had become progressively larger up to the present time. She had slight discomfort but no pain. Her menses began at the age of 12 years, occurred every twenty-eight days and lasted four days. Her past history was not contributory. Examination revealed her temperature to be 98.8° F. The abdomen was enlarged and filled with a cystic mass which extended 5 cm. above the umbilicus. Recto-abdominal examination showed a large mass filling the entire pelvis. The white blood count was 7,200 cells per c.mm. with a normal differential count. X-ray examination of the abdomen was reported as negative.

The patient was operated upon on May 12, 1941, and a large ovarian cyst arising from the right ovary was found. Because of its size it was aspirated before it was removed and 2 L. of a serous fluid were suctioned off. Following this a right salpingo-oophorectomy was performed. The uterus and left adnexa were normal. The patient made an uneventful recovery and was discharged from the hospital on May 24, 1941. Follow-up examination to the present time has shown her to be in excellent health with no recurrence of the tumor.

*Pathologic Report.*—The specimen consisted of a large cystic mass weighing 1,720 grams and measuring 17 by 15 by 10 centimeters. Fibrous septa divided it into numerous small cysts. A small area on the surface showed papillary formation. The inner lining



of the cyst was smooth except for a few papillary projections. The contents of the cyst was a pseudomucinous type of fluid.

*Microscopic Examination.*—Section showed a cyst wall filled with characteristic pseudomucinous epithelium with a sudden transfer to papilliferous and irregular glandular epithelial tissue. In the latter zone the nuclei showed marked variation in size, shape, and orientation to the basement membrane. In another area a more solid, compact papilliferous cellular tissue was found with heaping up of epithelial cells and active mitoses. *Diagnosis:* Pseudomucinous cystadenocarcinoma of the ovary (Figs. 2 and 3).

*Comment.*—This girl's symptoms dated back over two years. The diagnosis of ovarian neoplasm was readily made when she presented herself at the hospital but it was only on microscopic examination of the cyst that its malignant nature was ascertained. Had it been known that this was a malignant tumor at the time of operation, it would perhaps not have been aspirated before removal, and a more radical procedure might have been employed. The question of postoperative radiation arose but the child's family refused further treatment. Thus far, after seven years, no recurrence has taken place.

**CASE 6.**—B. M., No. A52283. This 13-year-old white girl was admitted to the Queens General Hospital on June 3, 1942, complaining of nausea and vomiting of three days' duration. On May 31, 1942, after swimming she became nauseated and vomited and complained of a pain in the right lower abdomen. Her local physician examined her and, finding a large abdominal mass, sent her into the hospital. Her history revealed that two months previously she had her first menstrual period which lasted two weeks. She never had any vaginal bleeding before or after that episode. Her past history was otherwise not contributory. Examination in the hospital showed a well-developed and well-nourished girl in no apparent pain or distress. The temperature was 99° F., the pulse 80 per minute and the respirations 20 per minute. Secondary sex characteristics were normal for a 13-year-old girl. The positive findings were limited to abdominal and rectal examination which revealed a large, nontender mass filling the entire abdomen. The blood count was normal. Urological examination including x-ray films was normal. A preoperative diagnosis of ovarian cyst was made.

On June 12, 1942, the patient was operated upon and a large ovarian cyst filling the entire abdominal cavity and arising from the right ovary was found. There were about 2,000 c.c. of clear fluid in the peritoneal cavity. The cyst was not adherent but was twisted twice on its pedicle. The left ovary and the uterus were normal. A right salpingo-oophorectomy was performed and the patient made an uneventful recovery, being discharged on June 24, 1942. Follow-up examination to 1947 has shown no recurrence.

*Pathologic Report.*—The specimen consisted of an irregular, oval, soft cystic mass 17 by 16 by 11 cm. Numerous cystic cavities contained clotted blood, others contained a clear watery fluid. All the cavities were lined by a smooth layer of tissue. Between many of the cystic spaces a translucent, soft, yellow tissue was visible.

*Microscopic Examination.*—Section through some areas of tumor showed multilocular cystic foci, some containing blood, and lined by deep-staining, closely placed cells, which resembled granulosa elements in cytology. Some cysts had irregular papilliferous projections which showed a central vessel with radial arrangement of cells mindful of the cumulus oophorus. Some Call-Exner structures were also seen. The cells merged with adjacent stroma in many areas while in some zones the cellular cyst wall lining was sharply delineated. More solid portions of the tumor showed an edematous, fibrillar, and spindle-celled stroma which showed transition to more hypertrophied and hyperchromatic stromal-cell areas. In the latter areas particularly, considerable variation in size and shape of the nuclei was present. Some such areas showed lipoid material in the cytoplasm in abundance. In the cystic areas the nuclei were small and uniform. *Diagnosis:* Granulosa-cell tumor with anaplastic changes (Fig. 4).

*Comment.*—A correct diagnosis of ovarian neoplasm was made in this case. The symptoms of nausea and vomiting were probably due to the twisting of the pedicle which was also associated with sharp lower abdominal pain. Apparently the torsion of the pedicle was not



Fig. 2.

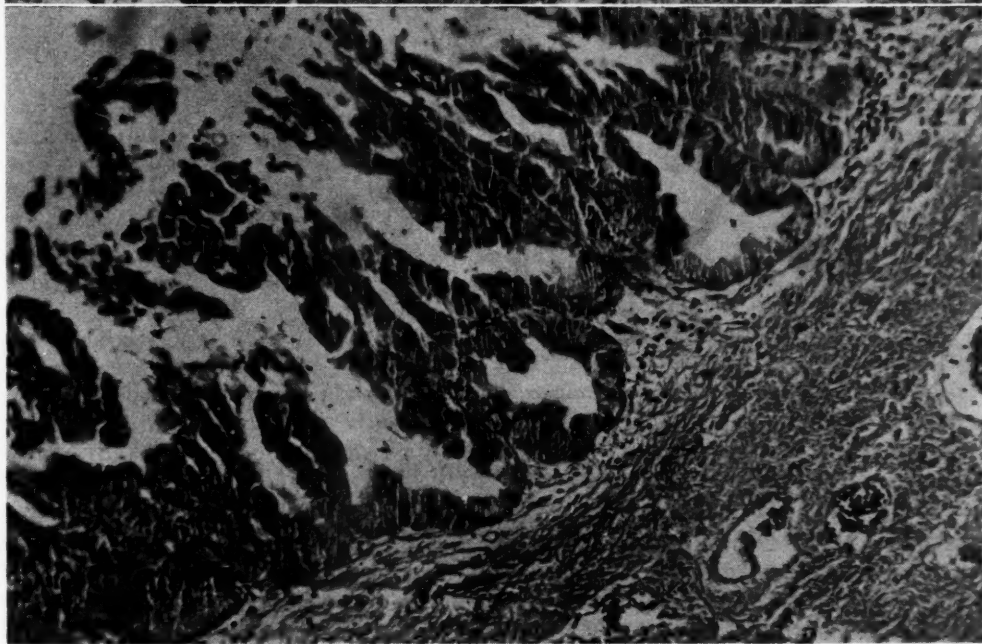
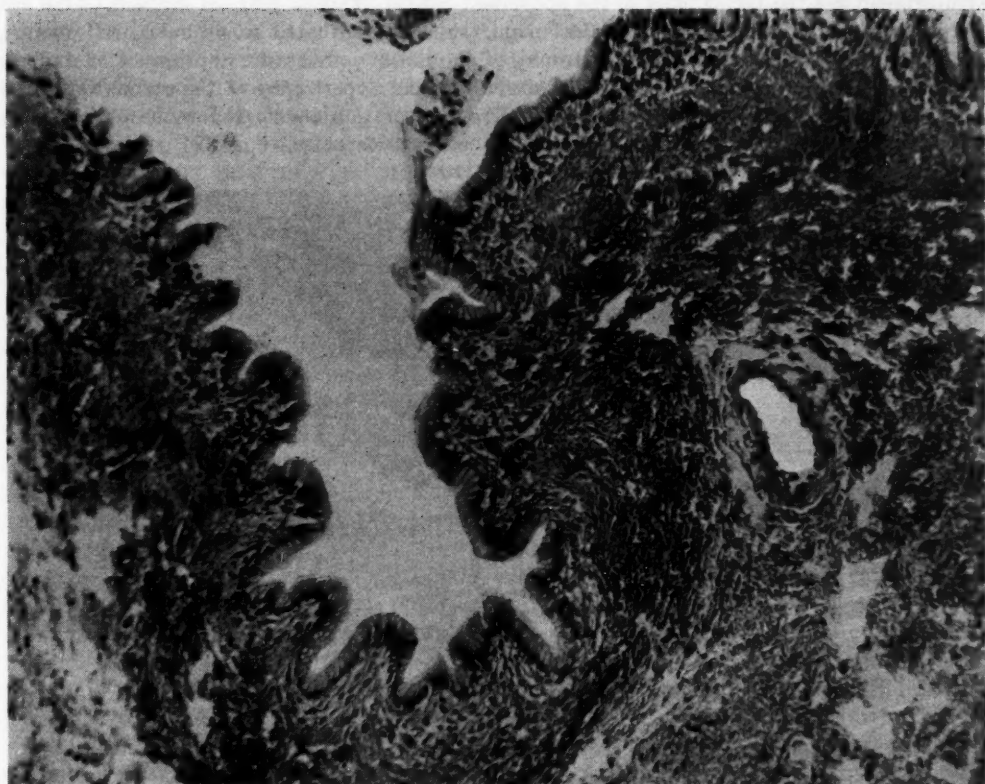


Fig. 3.

Fig. 2.—Pseudomucinous epithelial lining of cyst wall in a nonmalignant area. ( $\times 250$ .)  
Fig. 3.—Adenocarcinomatous area of cyst wall. ( $\times 440$ .)

complete or perhaps it untwisted in the few days before admission to the hospital. The only sign present was the tumor mass in the abdominal cavity. This 13-year-old girl was at the age of puberty so that none of the clinical manifestations attributed to granulosa-cell tumors, such as precocious menstruation, hypertrophy of the breasts, premature appearance of axillary and pubic hair, development of the external genitals and hypertrophy of the uterus were present. It was deemed advisable to be conservative at operation and to follow the patient carefully since the late recurrence of these neoplasms was considered.

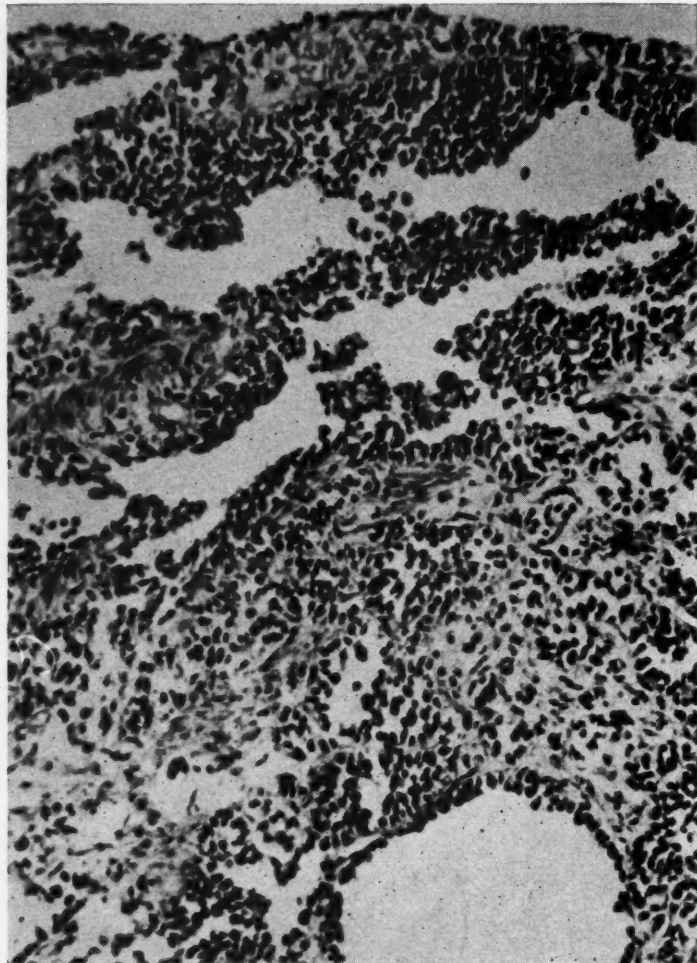


Fig. 4.—Area showing granulosa-cell tumor with cystic spaces resembling Graafian follicles. (×360.)

#### Discussion

Of the six ovarian neoplasms here reported, two were dermoid cysts, one was probably a dermoid, one was a simple luteal cyst, one was a pseudomucinous cystadenocarcinoma, and one was a granulosa-cell tumor. Torsion of the pedicle occurred in three cases and hemorrhage in three cases. Symptoms had been present for six months or longer in four of the cases and for several days in the two other cases. Pain was the most common symptom and was present in five of the six cases. The most frequent sign was the presence of a mass palpable on recto-abdominal examination, this also occurring in five

of the six cases. Three patients who had an elevated temperature had torsion or hemorrhage in the cyst but the one patient (Case 6) who had incomplete torsion did not have an elevated temperature. There was no alteration in the menstrual cycle in the three patients who were menstruating at the time the tumors were discovered. During the twelve-year period covered by this report, two other 14-year-old girls with functional ovarian cysts were operated upon because of an incorrect diagnosis of appendicitis. One girl had a hemorrhagic corpus luteum cyst measuring 6 cm. in diameter and the other had a cystic ovary containing many follicular cysts which measured 5 cm. in diameter.

In 1937 Witzberger and Agerty<sup>2</sup> collected all ovarian neoplasms reported in children up to 10 years of age. There were 186 cases of which 38 per cent were carcinomas or combined malignancies, 32 per cent were simple or multilocular cysts, 24 per cent were dermoids and 7 per cent were teratomas. Abt<sup>1</sup> states that 60 per cent of ovarian tumors in children are malignant, and Ladd and Gross<sup>10</sup> concur with this figure, adding that of the benign neoplasms 20 per cent are dermoids and 20 per cent are simple cysts.

The case of the youngest patient with a malignant tumor was reported by Ziegler.<sup>11</sup> This was in a 7-month stillborn fetus. The fetus weighed 1,280 grams and was delivered prematurely by breech extraction from a patient with a marginal placenta previa. Both ovaries were entirely replaced by carcinoma. Bulfamonte<sup>12</sup> reported the successful removal of a cystadenoma measuring 15 by 13 cm. from a 36-day-old infant who had presented signs of an abdominal mass since birth. These two cases occurring in infancy are mentioned to emphasize the fact that unless the possibility of an ovarian neoplasm is thought of, the diagnosis will be missed in infants. Since at least 20 per cent of ovarian neoplasms in children are dermoids, x-ray examination of the abdomen may reveal the presence of bone, teeth, calcified material or the translucency of the fatty contents, any of which would be an aid in diagnosis. Hemorrhage from a follicular or corpus luteum cyst should be considered in a girl showing signs of acute appendicitis and the ovary preserved, if at all possible, at operation.

The greatest incidence of granulosa-cell tumors is between 30 and 50 years according to Traut and Marchetti.<sup>15</sup> About 5 to 10 per cent occur before the age of puberty according to Dockerty.<sup>16</sup> One of our six cases had a granulosa-cell tumor but no abnormal clinical manifestations were present.

A freely movable tumor with a long pedicle may undergo torsion, which may occur suddenly or slowly and which may be complete or partial. Torsion results in occlusion of the thinner veins of the pedicle before the more resistant arteries are occluded, so that blood is able to enter the tumor but cannot escape. Perhaps torsion occurs more frequently in children because of their greater activity and because they are more likely to receive trauma to the abdomen or lift excessively heavy weights. Such intra-abdominal causes as vomiting and straining at stool are more common in children too. Taussig<sup>13</sup> states that torsion occurs in 28.6 per cent of the cases in children, a figure much higher than that given by Graves<sup>14</sup> who believes that twisting occurs in 10 to 20 per cent of ovarian tumors of all ages. Frequently, as in two of our cases, it is the torsion that makes known the presence of the tumor.

### Summary and Conclusions

1. Six cases of ovarian neoplasms in children have been reported. These occurred over a twelve-year period during which a total of 246 ovarian neoplasms were operated upon in adults and children.

2. Four of the neoplasms were benign, two malignant.
3. The most frequent tumor encountered was the dermoid cyst.
4. Complications such as torsion and hemorrhage occurred in four of the six cases.
5. The most common symptom was abdominal pain, which was present in five of the six cases.
6. The most reliable sign was palpation of a mass on recto-abdominal examination.
7. Unless the possibility of ovarian neoplasm is considered in the differential diagnosis of lower abdominal pain in children, the correct diagnosis will be missed.

We wish to thank Dr. Alfred Angrist, Pathologist at the Queens General Hospital, for reviewing the microscopic sections and for his suggestions in the preparation of this paper.

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## SUBMUCOUS MYOMA IN TERM PREGNANCY

HAROLD L. GAINES, M.D., AND JAMES E. KEELER, M.D., KANSAS CITY, MO.

A RECENT experience in dealing with a prolonged septic puerperal course of 30 days' duration due to an undiagnosed submucous myoma led to a survey of the literature. It was of note that the English literature of the last twenty-five years contained only four instances of similar cases. Duckering<sup>1</sup> reported a 35-day course, Kosmak<sup>2</sup> one of 30 days, and Fischmann<sup>3</sup> one of 26 days, in all of which the offending myoma presented vaginally. Eisaman<sup>4</sup> reported a 52-day septic puerperal course which was terminated by hysterectomy. If, as was true in our experience, the recognition of a solitary submucous myoma comes only after exclusion of all other possibilities with failure of therapeutic measures and is then revealed by intrauterine examination after much delay, this report may prove of some value.

Specific reports of the incidence and fate of submucous myomas in pregnancy are rare. In a total of 355,550 pregnancies reported in various series in the literature, 1,785 myomas were recorded (Table I), yet only four instances of submucous myomas in term pregnancy were found. This indicates either a rather rare complication of pregnancy or else a condition which is not commonly reported. This paper will include a report of three such cases which represent three of the possible outcomes of such a combination. Before presenting the cases, a review of the available literature in respect to myoma uteri and pregnancy is in order.

TABLE I. INCIDENCE OF FIBROMYOMA IN PREGNANCY

YEAR	AUTHOR	TOTAL PREGNANCIES	TOTAL FIBROIDS	PER CENT	CLINICALLY SIGNIFICANT	PER CENT
1923	Kosmak	33,269	114	0.34	114	0.34
1927	Pierson	30,836	250	0.81	191	0.60
1932	Watson	11,675	157	1.30	110	1.00
1933	Campbell	32,870	142	0.43	82	0.25
1934	Eisaman	23,541	71	0.30	71	0.30
1935	Mussey and Hardwick	5,105	97	1.90	97	1.90
1941	Willson	5,271	53	1.00	53	1.00
1941	Thompson	2,000	118	7.20	118	7.20
1943	Lazard	2,515	32	1.25	32	1.25
1946	Duckering	22,283	361	1.40	110*	0.49
Total		169,365	1,395	0.82	978	0.52
1886-1911	Lynch†	186,185	390	0.21		
Total		355,550	1,785	0.50		

\*Over 6 cm. in diameter.

†Compilation of seven authors.

**Incidence.**—In recent literature, the incidence of myoma uteri in pregnancy has been variously reported as ranging from 7.2 per cent (Thompson<sup>5</sup>) to 0.30 per cent (Eisaman). Mussey and Hardwick<sup>6</sup> reported 1.9 per cent in their

series but believe that this figure is higher than would normally be reported due to the fact that this complication of pregnancy is often referred to them for management. The figures are somewhat confused by interpretation as to what is to be considered a significant or clinically important fibroid. Thus, Duckering reports a total incidence of 1.4 per cent and separates those which are significantly larger (over 6 cm.). These constituted 0.49 per cent. Watson<sup>7</sup> reported an over-all incidence of 1.3 per cent but after excluding those myomas so small as to be considered insignificant this figure is corrected to 1 per cent. Pierson's<sup>8</sup> total incidence of 0.81 per cent was reduced to 0.6 per cent by exclusion of those considered too small to be important. Campbell's<sup>9</sup> series showed an incidence of 0.25 per cent of clinically significant myomas although this figure was raised to 0.43 per cent when all fibroids diagnosed were included. Other series reported were Willson,<sup>10</sup> 1 per cent, Lazard,<sup>11</sup> 1.25 per cent, Kosmak, 0.3 per cent, with all myomas reported in these series considered of clinical importance. Lynch,<sup>12</sup> in 1913 in an excellent review of the literature to that date, stated that the condition is not uncommon and that the proportion in various obstetrical clinics ranges between 1:125 and 1:2000. In 186,185 pregnancies reported by seven authors between the years 1886 and 1911 and quoted by Lynch, there were 390 myomas, an incidence of 0.21 per cent. In the years between 1923 and 1946, ten authors reported a total of 1,395 fibroids in 169,365 pregnancies, an incidence of 0.82 per cent. Of these, 978, or 0.52 per cent, were clinically significant. The difference in the incidence of 0.21 per cent reported by Lynch and this figure may represent the improvement in diagnostic skill in this period. There is no doubt that myoma uteri may co-exist with pregnancy in many cases and be unrecognized so that the probable incidence of this association is near 1 per cent.

On the basis of the series mentioned above, the commonly discussed complications or results of myoma uteri and pregnancy may be considered under the following headings: Relation to Sterility; Relation to Abortion; Disturbances During the Course of Pregnancy; Disturbances in the Mechanism of Labor and Immediate Postpartum Course; and Effects of Pregnancy on the Myoma.

*Relation of Myoma Uteri to Sterility.*—Sterility in a group of apparently normal women in the childbearing age has been variously estimated as ranging from 7 per cent to 17 per cent. Lynch believed that approximately 25 per cent of married women in the childbearing age with fibroids are sterile. Studdiford<sup>13</sup> quotes Graves as saying that the average incidence of sterility in an unselected group of women in the childbearing age is 10 per cent to 15 per cent and that this figure rises to 30 per cent in women with myoma uteri. Watson states that 37 per cent of his series had early abortions or prolonged periods of sterility prior to conception. Eisaman reports that 25 per cent of the women in his series had a relative period of sterility before becoming pregnant. Campbell reports that 40 per cent of the primiparas in his series became pregnant only after long periods of sterility. Only eighteen patients in his series had living children and twenty-six (32 per cent) had histories of repeated immature births. Duckering, on the other hand, in 160 primigravidas, found no evidence of infertility. She points out that too many factors in causation of sterility are unrecognized to allow accurate analysis of any group of women.

*Relation to Abortion.*—Gusserow in 1886, quoted by Lynch, reported that abortion occurs in 21 per cent of pregnancies complicated by myoma uteri. In a review of eight series of cases totaling 1,001 pregnancies associated with myomas, figures varied from 4 per cent by Thompson to 17.1 per cent by Duckering with an average incidence of 13.8 per cent. This figure strikes a medium ground between the extremes but is still higher than in an unselected

group of Duckering's in which the rate was 8 per cent. The New York Birth Control Clinics report abortions in 27 per cent of total recorded pregnancies. These figures include spontaneous and induced abortions and, if the latter constitute two-thirds of the total as generally stated, the figure of 8 per cent for spontaneous abortion seems logical. Thus, the combined figures of these series represent a 50 per cent increase in the myoma uteri over normal.

TABLE II. ABORTIONS IN PREGNANCIES COMPLICATED BY FIBROMYOMA

YEAR	AUTHOR	NO. CASES	NO. ABORTIONS	PER CENT	REMARK:
1923	Kosmak	114	11	9.7	Two in first trimester, 20 mid-trimester
1927	Pierson	191	22	11.5	
1933	Campbell	82	12	14.6	
1934	Eisaman	71	9	12.6	
1935	Mussey and Hardwick	97	12	12.4	
1941	Willson	53	8	8.8	
1943	Lazard	32	2	6.2	
1946	Duckering	361	63	17.1	45, or 12.4 per cent, spontaneous
Total		1,001	139	13.8	

*Disturbances During Pregnancy.*—A number of reports are available as to the disturbances that may be encountered during pregnancy complicated by myoma uteri. Outstanding are the problems introduced by aseptic necrobiosis in the growth, hemorrhage associated with abortion, and torsion of pedicle. The infrequency with which these problems are met makes the experience of others most valuable.

TABLE III. DISTURBANCES DURING PREGNANCY

YEAR	AUTHOR	NO. CASES	DISTURBANCES IN PREGNANCY	PER CENT	REQUIRING SURGERY	PER CENT
1934	Eisaman	71	5	7.1	4	5.6
1935	Mussey and Hardwick	97	45	46.5	32	33.0
1941	Willson	53	8	15.1	8	15.1
1941	Thompson	118	23	19.5	3	2.5
1946	Duckering	361	40	11.0	4	10.0
Total		700	121	17.3	51	7.28

A group of articles by five authors is used for study of the frequency with which difficulty may occur. There were a total of 700 cases of pregnancy associated with myoma uteri, 17.3 per cent of which produced definite clinical pathological states, 7.28 per cent requiring surgical intervention.

In relation to the problem of interference during pregnancy, a number of opinions have been expressed. Studdiford believes that myomectomy should not be performed on the pregnant patient since it only adds to what is an already definite tendency toward abortion. Huber and Hesseltine<sup>14</sup> concur in Studdiford's opinion. Faulkner,<sup>15</sup> in a study of the pathological physiology, states that, "Sufficient circulation usually remains or is restored so that breakdown and liquefaction are rare and recovery ensues if an expectant course is pursued."

*Premature Labor.*—Available figures give an increased incidence of two to ten times the normal for premature labor in pregnancies associated with myoma uteri. Duckering reports 5 per cent, Mussey and Hardwick 6.2 per cent, Thompson 22 per cent, Eisaman 14 per cent, Kosmak 20 per cent, and Campbell 24.4 per cent, for an average incidence of 12.3 per cent.

TABLE IV. PREMATURE LABOR IN PREGNANCY COMPLICATED BY FIBROMYOMAS

YEAR	AUTHOR	CASES	PREMATURE	
			LABOR	PER CENT
1923	Kosmak	114	23	20.1
1927	Pierson	191	19	10.0
1932	Watson	157	24	15.3
1933	Campbell	82	20	24.4
1934	Eisaman	71	10	14.0
1935	Mussey and Hardwick	97	6	6.2
1941	Thompson	118	26	22.0
1946	Duckering	361	18	5.0
Total		1,191	146	12.3

The generally accepted figures for normal in this respect may be given as: vertex 95 per cent, breech 3.1 per cent to 3.9 per cent, face 0.34 per cent to 0.6 per cent, and transverse, 0.56 per cent to 0.96 per cent.

The literature here reviewed would seem to bear out the generally accepted belief that pregnancies complicated by myoma uteri tend to result in a higher incidence of abnormal presentations. Breech presentation is increased from two (Duckering) to seven times (Lynch) over normal. Transverse presentation is from two (Duckering) to eight times (Campbell) more frequent.

TABLE V. INCIDENCE OF PRESENTATIONS

AUTHOR	CEPHALIC		BREECH		TRANSVERSE	
	(PER CENT)		(PER CENT)		(PER CENT)	
Lynch	59.0		22.0		18.0	
Pierson			19.0			
Campbell	64.4		10.0		4.8	
Willson	93.0		5.3		2.6	
Thompson	95.84		4.16			
Duckering	90.6		6.7		1.3	

*Disturbances in Labor.*—It has been generally stated that myoma uteri causes prolonged labor due to faulty uterine contractions and uterine inertia. Studdiford states that difficulties in labor may be encountered due to faulty uterine mechanisms. Authors reviewed here leave some doubt concerning this problem. Thompson reported that labors in general were no longer except in those with abnormal presentations and concludes that fibroids cause prolonged labor only in so far as they cause abnormal presentations. Duckering reported that 9.1 per cent of her patients had prolonged labors and that 6.1 per cent had precipitate labors which was exactly the same as the general clinic average. Willson, after slight qualification, concluded that the averages for all groups were well within normal limits.

Postpartum hemorrhage is another generally accepted complication of pregnancy associated with myoma uteri. This is usually blamed on atony of the uterus due to the presence of the fibroids. Eisaman and Studdiford both state that postpartum hemorrhage is more common in these patients although no figures are given. Thompson states that hemorrhage greater than average occurred in 12.7 per cent of his 150 deliveries of women with fibroids, although only one-fourth of these were considered definitely large, the other three-fourths being classified as moderate but greater than average. Willson states that hemorrhage is more frequent, based on the fact that in his series 20 per cent lost over 300 c.c. of blood although none lost more than 500 c.c. Watson saw



postpartum hemorrhage in only 2.75 per cent of his series. Mussey and Hardwick reported postpartum hemorrhage in 5.1 per cent of their patients. Campbell reports hemorrhage in 31 per cent of eighty-two large fibroids following delivery and Pierson reported excessive bleeding in 33.6 per cent of his cases. Neither of these authors give the amount of blood loss that is designated as postpartum hemorrhage. Duckering reported that ten patients or 3.8 per cent of her series had postpartum hemorrhage. This is compared with the clinic average for the years in question which ranged from 1.5 per cent to 4.4 per cent. Five of the ten cases were attributed to atony, although in all cases the fibromyoma was so small as to be discovered only after the pregnancy. The other five were attributed to other causes. All in all, the question of myoma uteri as the causation of postpartum hemorrhage would seem to be open to some reasonable doubt.

*Effects of the Pregnancy on the Myoma.*—This may most conveniently be considered under two main headings: the effect of pregnancy on growth of the tumor; and degeneration of the tumor during pregnancy. Popular opinion has been that pregnancy exerts a marked effect upon tumor growth. Lynch, in his review of this subject, points out that most writers believe that the fibroid grows rapidly under the influence of pregnancy and involutes correspondingly after the termination of the pregnancy. He believes, however, that edema rather than true growth is involved. Reis and Sinykin<sup>16</sup> believe that myomas increase in size during pregnancy and point out that this has been variously attributed to: (1) hypertrophy and edema of the tumor; (2) hyperplasia and edema of the tumor; and, (3) actual growth concomitant with uterine growth. Wheritt<sup>17</sup> and Kosmak both believe that tumor growth is rapid during pregnancy. Emge,<sup>18</sup> in his study of the growth of various tumors during pregnancy, stated that tumor growth is dependent upon two main factors: (1) the inherent growth factor of the tumor tissue; and, (2) the resistance factor in the host. He stated that in fibroids there may be some muscle hypertrophy plus edema and increased vascularity, but cautions that Bornes' theory of tumor migration deserves serious consideration in the apparent growth of these tumors. This is borne out by the work of Randall and Odell,<sup>19</sup> who made careful histological studies of a series of seventeen specimens of fibromyomas removed from pregnant women. They found no evidence of either hyperplasia or hypertrophy of the tissue elements and insufficient edema to account for growth. They believe that the growth of these tumors is more apparent than real and that thinning of the uterine wall plus migration of the tumor makes them more easily palpated. Evidence from the literature is therefore inconclusive and even arouses some doubt as to the enlargement of the fibroids in pregnancy.

Degeneration of fibroids is a less controversial subject, most writers agreeing that this occurs frequently during pregnancy. Willson states that red degeneration usually occurs in the second trimester of pregnancy. He believes that the fibroids outgrow their blood supply and become relatively avascular. Wheritt also believes that this complication usually takes place in the mid-trimester and that the prognosis is uniformly good. Brindeau<sup>20</sup> believes that degeneration of fibromyomas is very common during pregnancy and that it seldom produces severe disturbances. Polak<sup>21</sup> states that red degeneration is common in pregnancy due to the rapid growth of the tumor which causes it to outstrip its blood supply. Watson concurs with this, believing that the lesion is a vascular one which is followed by gray necrosis and liquefaction. The process is usually sterile but may be complicated by secondary infection from the uterine cavity. He found this lesion in twenty-three of forty-one patients examined. Eisaman found that 69 per cent of

fibroids removed from pregnant women showed necrosis, as opposed to 45 per cent of a control group of nonpregnant women. Campbell reports that 76 per cent of the myomas removed from pregnant women showed necrosis as against 7.8 per cent of a control group. He believes that necrosis is usually due to trauma, thrombophlebitic changes, and interruption of the blood supply during labor. He also believes that infection plays an important part with two main factors operative: (1) a low-grade infection which lies latent in the tumor until lowered resistance and blood supply allow it to spread; and (2) infection ascending by venous and lymphatic channels following operative obstetrical procedures. Contributory factors are prolonged labors, early rupture of the membranes, adherent placenta, and subinvolution of the uterus. Lynch stated that submucous growths tend to degeneration in the puerperium due to trauma resulting from operative procedures. Pierson also takes this view and Duckering reports a morbidity of 15.4 per cent in the puerperium of pregnancy complicated by myoma uteri, a figure much higher than normally encountered. Reis and Sinykin point out that the overwhelming majority of fibroids complicating pregnancy have no clinical significance and that degeneration complicating such tumors is uncommon. They believe that only an occasional subserous or pedunculated myoma undergoes degeneration and that acute infection is uncommon.

### Case Reports

**CASE 1.**—R. C., 33-year-old gravida iii, para i. Last menstrual period Sept. 1, 1946. Estimated date of confinement June 8, 1947. Both previous pregnancies terminated prematurely, the first at eight months with the delivery of a 5-pound living child and the second at five months. General physical examination was normal, and the pelvis was obstetrically adequate with the uterus enlarged to a size commensurate with the duration of the pregnancy at the time of her first visit. Laboratory examinations of urine and blood were within normal limits. Her prenatal course was uneventful, with mild nausea and vomiting during the early months and no complaints of bleeding, cramping, or abdominal pain. On June 13, 1947, the membranes ruptured and the patient began spontaneous labor. Three hours later she was delivered of a normal female infant after right mediolateral episiotomy. Placenta was delivered in eight minutes by simple expression. The blood loss was 60 c.c. measured.

Five hours after delivery she began to complain of abdominal cramps and passed a piece of tissue measuring 5 by 3 cm. Following this the postpartum course was normal and the patient was released on the seventh postpartum day. On subsequent visits she has been in good health.

**Pathological Report:** The specimen is an oval-shaped tumor mass measuring 5 by 3 cm. with a small pedicle-like appendage at one edge. Cut section reveals the whorled characteristics of fibromyoma with the marginal portion somewhat hemorrhagic. Section reveals degenerated intertwining bundles of smooth muscle and fibroblastic cells. Areas of high cellularity suggesting rapid growth are seen while in other areas early necrosis is taking place.

**Diagnosis:** Rapidly proliferating edematous fibromyoma with early necrosis and degeneration.

**CASE 2.**—B. M., 29-year-old gravida ii, para i. Last menstrual period April 5, 1942. Estimated date of confinement Jan. 12, 1943. Her first pregnancy had been eight and one-half years earlier and terminated with the delivery of a normal full-term child. General physical examination was normal, obstetrical pelvis was adequate, and the uterus conformed in size to the menstrual dates. Laboratory examinations on blood and urine were within normal limits. Her prenatal course was entirely normal. There was no nausea or vomiting and no complaints of vaginal bleeding, cramping, or abdominal pain. On Jan. 13, 1943, her membranes ruptured spontaneously and on Jan. 20, 1943, she was admitted to the hospital in active labor.

After five hours and forty-nine minutes she delivered a 3,050-Gm. child. The presentation was breech. The placenta was delivered three minutes later by simple expression. A second degree laceration was repaired. Total blood loss was 125 c.c. estimated.

The immediate postpartum course was normal. On the fifth postpartum day the temperature rose to 99.4° F., and on the following day to 100.4° F. following which she ran a mildly febrile course until discharge to home bed rest on the ninth postpartum day. The patient reported no further difficulty until Feb. 19, 1943, when she began to complain of severe cramps. These continued for a week and she then began to bleed vaginally and became conscious of a mass in the vagina which obstructed the flow of urine unless pushed up out of the way. On March 5, she was admitted to the hospital. Upon admission, physical examination and laboratory tests were normal except for a white blood cell count of 13,300 with a normal differential. Temperature was 99° F., pulse 82, and respiration 22. On the following day a pelvic examination was done disclosing a mass in the vagina which filled the vault and could be differentiated from the fundus. Following the examination the patient had a severe chill and the temperature rose to 103° F., pulse 140, and respiration 28. She was given sulfathiazole, 7½ grains every four hours but the temperature course remained septic. On March 10 she was prepared for surgery. Examination under anesthesia revealed a tumor mass estimated as 10 cm. in diameter extending from the cervical canal. This mass was soft in consistency and foul smelling. The tumor was removed in two portions, with a third portion inside the os being left when severe bleeding was encountered. The uterus was packed and the patient was returned to bed. The temperature fell by lysis during the post-operative period and on March 20, 1943, she was released from the hospital. She has subsequently (1947) been delivered of a full-term male infant after a pregnancy and labor without complication.

*Pathological Report:* The specimen consists of two roughly oval pieces of tissue the larger of which measures approximately 4 cm. in diameter. The external surfaces are roughened and the tissue has a foul odor. The larger specimen on section presents the reddish-brown appearance of muscular tissue, around the periphery of which there is a greyish-green necrotic appearing material. The consistency is generally soft. Section shows intertwining masses of muscular and fibrous tissue in which the latter predominates. There is considerable degenerative change including edema of the tissue, hyaline degeneration, necrosis, small areas of myxomatous change, and some areas of calcification. There is a profuse infiltration of polymorphonuclear leucocytes and mononuclear leucocytes with dense clumps of these cells in some areas.

*Diagnosis:* Fibromyoma showing extensive degenerative change and infection.

CASE 3.—D. M., a 24-year-old gravida i, para 0. Last menstrual period Jan. 14, 1947. Estimated date of confinement, Oct. 21, 1947. Past history was negative as concerned menstrual difficulties. Physical examination was negative. The pelvis was obstetrically adequate and the uterus was enlarged to the size of a six weeks' pregnancy in accordance with her menstrual history. Laboratory examinations of blood and urine were negative. Blood pressure was 140/70. The early prenatal course was uneventful. There were no complaints of vaginal bleeding, cramps, or abdominal pain. However, on Oct. 6, 1947, blood pressure was 140/98. Albumin was not present in the urine. In spite of medical management there was no improvement and on October 28 she was admitted to the hospital. Blood pressure was 170/100 and the urine showed 2 plus albumin. Continuation of conservative treatment elicited no improvement. Attempts at medical induction of labor failed and on November 5 the membranes were ruptured. After a latent period of about three hours contractions began and after a rapid labor of one hour fifty minutes she was delivered spontaneously of a normal female infant. Fifteen minutes later the placenta was delivered by simple expression. The blood loss was 120 c.c. measured and estimated.

*Puerperium:* Patient was placed on 50,000 units of penicillin every three hours prophylactically immediately after delivery. In spite of this she developed a febrile course beginning on the third postpartum day. There were no subjective complaints except those due to tem-



perature elevation. Physical examination was negative except for a symmetrically enlarged uterus with no tenderness or pain. Lochia was normal. After seven days penicillin was discontinued. On the ninth postpartum day, penicillin therapy was reinstituted with 100,000 units every three hours. Three days later the urine revealed a culture of gram-negative rods. Sulfathalidine, 15 grains every four hours, was prescribed. Temperature rose to 103° F. on the thirteenth postpartum day and 105.4° F. on the fourteenth postpartum day. Penicillin was increased to 100,000 units every two hours and streptomycin, 3 Gm. daily in divided doses was instituted. She was also given 250 c.c. whole blood transfusions every other day until five had been given. The streptomycin therapy was discontinued after nine days, but the penicillin was continued, 100,000 units every two hours.

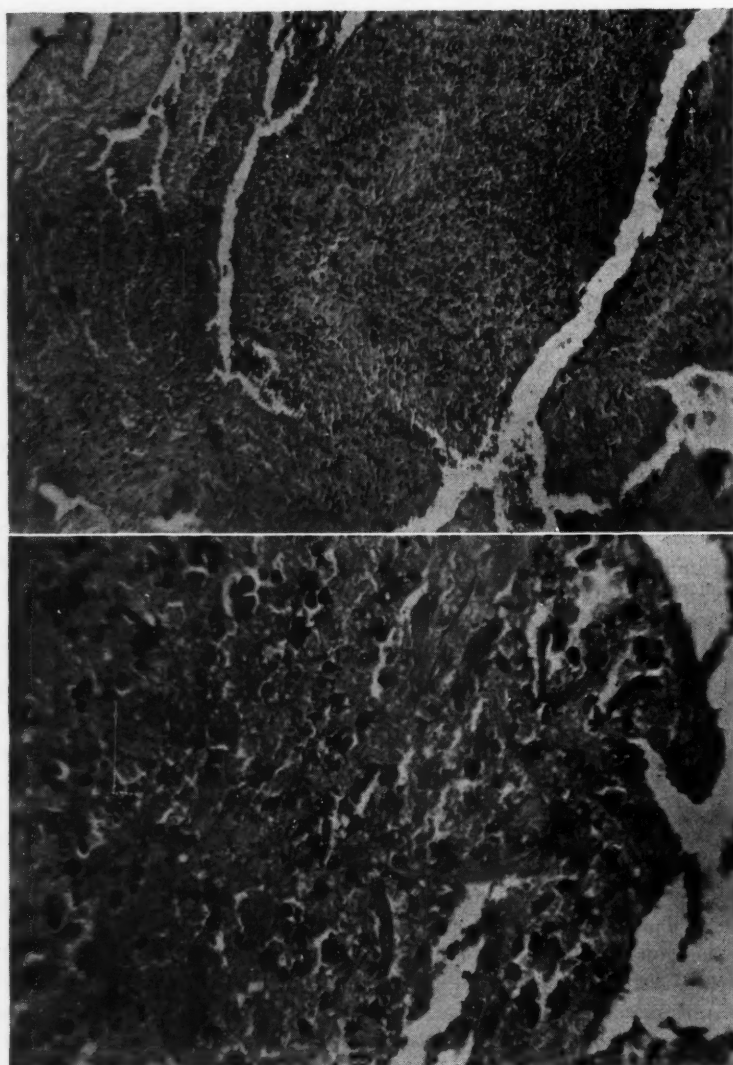


Fig. 1.—Low-power photomicrograph of friable cervix found in Case 3. Note necrosis of cervical gland mucosa and cervical stroma with acute inflammatory infiltration.

Fig. 2.—High-power photomicrograph of endocervix in Case 3 showing in better detail the extensive necrosis and acute inflammatory reaction.



Throughout this period of twenty days of morbidity treated with what may be considered adequate doses of antibiotics, small transfusions and one course of sulfathalidine, no improvement was noted. Physical findings remained negative except for a uterus which remained 2 cm. below the umbilicus with no demonstrable tenderness. Laboratory findings, including blood cultures, were negative except for leucocytosis with increase in immature forms.

On the twenty-third postpartum day the patient was taken to the operating room with a preoperative diagnosis of retained secundines and possible degenerating submucous fibromyoma. The cervix was found to be soft and almost completely effaced. With ring forceps a small amount of what appeared to be necrotic membranes was removed. Digital examination of the uterus then revealed a large submucous fibromyoma on a broad base which began about 2 cm. above the internal os of the cervix and involved the left lateral and anterior uterine walls. Cultures taken from the uterus at this time were reported as negative for growth. The tissue was reported as necrotic retained products of conception.

Following operation the patient's course showed no change. Penicillin was continued. On the twenty-fourth postpartum day the patient began to bleed vaginally in rather large amounts. This continued the following day. Further temporization was considered dangerous and surgery was elected. The uterus was found enlarged uniformly and symmetrically to a size of about 16 by 14 cm. and was extremely firm in consistency. The cervix was completely effaced and on the anterior and right portions was necrotic and friable. Both adnexa were negative although the left was bound rather firmly to the posterolateral aspect of the uterus. A supracervical hysterectomy and left salpingo-oophorectomy were performed. The patient was transfused and placed on penicillin and streptomycin in the dosage previously employed. After a brief rise to 104° F. on the first postoperative day the temperature fell by lysis, reaching normal on the fifth postoperative day. Medication was discontinued and the patient made an uneventful recovery and was released on the twelfth postoperative day. She has remained well for the four months following.

*Pathological Report:* The specimen consists of a uterus which measure 16 by 14 cm. and is symmetrically ovoid and smooth in contour. Occupying the entire endometrial cavity there is a large leiomyoma. On section the tumor mass is markedly reddish in color and bulges. In consistency it is rather soft with numerous areas of softer, more hemorrhagic character resembling degenerative change. Sections taken through the friable tissue of the cervix show marked edema and necrosis with a variable amount of inflammatory reaction of a nonspecific type (Figs. 1 and 2). Cell outlines are somewhat indistinct and nuclei in many instances are small and pyknotic. Sections through the uterus show the endometrium and myometrium to be atrophic. There is some hemorrhage in the myometrium and occasional small collections of inflammatory cells are observed in the endometrium. Sections through the tumor itself show the classical picture of leiomyoma with areas of hemorrhagic degeneration. Cultures of the uterus and the tumor mass are reported as showing no growth after seven days.

*Diagnosis:* 1. Endocervix showing inflammatory reaction, nonspecific in character; 2. Leiomyoma, intramural, with secondary degeneration; 3. Subacute endometritis and metritis.

### Discussion

These three cases demonstrate three of the possible outcomes of pregnancy complicated by the presence of submucous fibromyoma. Few similar cases are reported in the English literature of the past twenty-five years. Duckering reports one case of a 29-year-old primigravida with breech extraction at term followed by intrauterine infection and a septic course. On the thirty-fifth postpartum day a necrotic myoma presented at the introitus and was removed by vaginal myomectomy. Kosmak reports one case of a patient who was delivered vaginally at term and who after a mildly septic course for one month expelled a necrotic submucous myoma after administration of a course of ergot. Fischmann reports a case of a 40-year-old primigravida who was delivered at term by low forceps after a prolonged labor. An

adherent placenta was removed manually, in the course of which procedure a large submucous myoma was discovered. After a septic course of twenty-four days during which she received fluidextract of ergot in an attempt to promote expulsion of the myoma she was delivered vaginally of a necrotic, suppurating fibromyoma which measured 25 by 10 by 10 cm. Eisaman's case followed a seven-month premature delivery and necessitated a hysterectomy after fifty-two days of morbidity. He states, "Absorption from . . . a degenerating tumor is likely to produce a picture of severe infection beginning one or two weeks after delivery. . . . These symptoms may continue at length with prostration and anemia until the tumor has sloughed free from its attachments or has been extruded through the cervix permitting manual removal." Pierson reports one case of full-term pregnancy followed by the vaginal passage of a necrotic 12-cm. fibromyoma one week postpartum.

More frequently in the literature submucous or subserous fibromyomas are indicted in the causation of postabortal infections. Eisaman reported one such case after a four-month abortion in which the submucous fibromyoma became necrotic and sloughed. In Campbell's series five patients required myomectomy in the puerperium because of necrotic tumors although he does not specify whether they were submucous or subserous. Three of his cases were postabortal. In Duckering's series one vaginal myomectomy was done following an eight-week abortion because of infection. Watson performed hysterectomies seven times in the puerperium but as the earliest was done some two months after delivery these may be assumed to have been elective rather than indicated by sepsis or necrosis. Pierson also reports two cases of postpartum hysterectomy but does not specify the indications. The same is true of Kosmak's two cases of hysterectomy performed in the puerperium.

According to Studdiford, in cases delivered by the vaginal route it is not uncommon to see acute degenerative changes arising during the early postpartum period with a marked possibility of secondary infection. He states, "If the pain is marked and the fever high, especially if the tumor is submucous or intramural, immediate hysterectomy should be performed."

Regarding hysterectomy versus myomectomy in the puerperium, Huber's experience and analysis of literature revealed the former to be a much safer procedure. The mortality given by him for hysterectomy in the puerperium was 3.4 per cent and 12.8 per cent for myomectomy.

In light of the conclusions brought out in the review of the literature, it is interesting to emphasize several points in the above cases. The first case had had two previous pregnancies terminate early, one by premature delivery, and the other by late abortion. Case 2 had what may be considered as eight years of relative infertility following her first delivery. Whether these can be attributed to the presence of unsuspected fibromyoma is problematical. In none of these three pregnancies was myoma uteri suspected either before or during pregnancy and labor. This is probably true of submucous myomas and accounts for the paucity of reports concerning them in the literature.

Another point worthy of note is that all three of these cases had comparatively rapid and easy labors and deliveries. In none was there any excessive instrumentation. In all three cases the membranes were ruptured prior to labor, once artificially and twice spontaneously. Blood loss was below average in all three cases and the placentas in all cases were delivered easily and without manipulation.

It is difficult in Case 3 to account for the septic course run by the patient after delivery on the basis of what was found at surgery. The tumor itself showed only mild degenerative changes which seem hardly sufficient to account for the highly febrile course. The main findings were not in the tumor

itself but in the endocervix and parametrium on the opposite side from the attachment of the tumor. These changes consisted of necrosis due to pressure and what is described as nonspecific inflammatory changes. In view of the repeated negative cultures from the cervix and the uterus, the pathological changes must be accepted. Yet the response to surgery certainly indicates that the septic focus was removed. Campbell believes, as stated elsewhere, that secondary infection may ascend by venous and lymphatic channels from below or that the tumor may represent a focus of low-grade infection which lies dormant until the trauma incident to delivery and the decreased blood supply due to involution permit its spread. Neither of these possibilities could be demonstrated in this case.

In passing it is also interesting to note that, in the first case, the pathologist called attention to the increased cellularity of some areas suggesting rapid proliferation and growth of the tumor. This is not in accord with the findings of Randall and Odell reported above.

### Summary

1. Three case histories are reported which demonstrate three of the possible outcomes of term pregnancy complicated by submucous myoma uteri.
2. The literature of the last twenty years is reviewed.

We wish to express our appreciation to Dr. Milton B. Casebolt, Kansas City, Mo., for permission to use one of his cases in the preparation of this paper.

### Addendum

Since the presentation of this paper, Dr. William W. Curtis, Springfield, Illinois, has reported one further case to us, an abstract of which follows:

A 28-year-old gravida iii, para ii, had an uneventful prenatal course. On April 23, 1948, she was delivered spontaneously of a 2,950 Gm. infant after manual rotation. On April 25 the patient complained of unusually severe cramps and passed a small, ovoid tumor, 4 by 4 by 7 cm., which was diagnosed histologically as a fibromyoma with a small central area of necrosis. The patient had an afebrile puerperium with no excessive bleeding or other unusual symptoms and was discharged on her eighth postpartum day.

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## **FETAL MORTALITY ASSOCIATED WITH THE METHOD OF DELIVERY OF PATIENTS WITH PLACENTA PREVIA**

L. V. DILL, M.D., J. B. SHEFFERY, M.D., AND PRENTISS WILLSON, JR., M.D.,  
WASHINGTON, D. C.

*(From the Department of Obstetrics and Gynecology, Georgetown University School of  
Medicine, Columbia Hospital for Women, and the Yater Clinic)*

**P**RIOR to the extensive use of the cesarean section as a "safe" method of delivery for patients with placenta previa, vaginal delivery was routinely used. The maternal mortality was reported as varying from 5 to 20 per cent, and the fetal mortality from 40 to 70 per cent.<sup>1-5</sup>

Cesarean section has assumed a dominant place in the treatment of this serious complication of pregnancy and in the last twenty years the maternal mortality has dropped to 1 to 5 per cent.<sup>6-10</sup> Although general opinion has almost completely turned from vaginal delivery of these patients, a few individuals have continued the practice. One investigator states that he has never delivered a patient with placenta previa by cesarean section,<sup>11</sup> while another states that he rarely finds abdominal delivery necessary for patients with this complication.<sup>12</sup>

It is our belief that cesarean section is still not an innocuous procedure even in practiced hands, that not only is the immediate risk much greater but also remote complications of abdominal laparotomy and rupture of the uterus add definitely to the hazards of the procedure. We feel that vaginal delivery whenever possible is in the best interests of the mother, provided that neither mother nor baby is exposed to undue risks.

With the advent of blood banks, methods of introducing fluid into the vascular system at rapid rates, antibiotics, chemotherapy, and the extraperitoneal approach to the uterus, it seems logical that much more latitude than previously existed is possible in the treatment of most of the complications of pregnancy. We are unable to find controlled data concerning the risk to the fetus under these new techniques in the treatment of placenta previa.

In this communication the delivery of patients with placenta previa by the vaginal route utilizing modern methods of combating shock and infection is compared with delivery by abdominal section in an effort to stimulate further investigation of this vitally important subject.

### **Materials and Methods**

Fifty consecutive patients who had placenta previa and were delivered vaginally represent the experimental group. It must be clarified that during this time, seven cesarean sections were done in this institution, on patients



with placenta previa, but that these patients in no way differed from those delivered vaginally.

The diagnosis of placenta previa was made in all instances by vaginal examination and, in all, placental tissue was found to be extending over some portion of the external os. No instance of low implantation of the placenta was considered in this series, for although this is merely a less obvious state of the same process, the problems to be solved and the method of handling them would be in no way comparable to those of true placenta previa.

The degree of previa was classified as complete or incomplete. We feel that the method of classification of this condition as marginal, partial, and central is unsatisfactory, for except in the very rare instance of a central placenta previa the amount of placental tissue covering the cervical opening is merely a function of time and cervical dilatation.

The method of delivery varied as to the size of the baby, the amount of bleeding, the degree of completeness of the placenta previa, the configuration of the lower uterine segment, and the presence of other maternal complicating factors. In general, patients whose fetuses were previable or borderline in viability, as determined by the expected date of confinement and the estimated weight of the baby, were allowed to remain in the hospital following a sterile vaginal examination which was done to render a diagnosis of the cause of bleeding but which was carefully and gently carried out to prevent displacement of placental tissue. The decision to deliver these patients and the choice of method were made at the onset of severe bleeding or of labor, whichever process supervened.

Membranes were ruptured whenever possible in the delivery of patients with viable babies or those with previable babies who were definitely in labor or bleeding excessively. If this procedure was not possible in the *previable stage*, the placental edge was perforated and a Hicks version done in a vertex presentation, a foot pulled down in a breech. There was only one complete previa found near term which did not become incomplete with labor; this patient had a cesarean section and is not included in this series.

As for patients with viable fetuses who were in labor but not bleeding excessively, if no clear membrane could be found, they were allowed to continue in labor with close observation. Delivery was effected at complete dilatation, or membranes ruptured at the appearance of clear membrane. At the onset of sudden bleeding, a decision would be made immediately.

Adjuncts to rupture of the membranes such as the Willett clamp and the Beck binder were used in those cases in which the uterine forces were not considered sufficient to apply the fetal head closely to the cervix. Pituitrin in  $\frac{1}{2}$  minim doses was used to stimulate contractions in those cases with inefficient or no labor.

For a control series we were fortunate in obtaining fifty records from a hospital in which cesarean section is done almost routinely on all patients with serious painless bleeding occurring in the last trimester of pregnancy. Records were taken consecutively on all cesarean sections done for placenta previa and performed by qualified and competent obstetricians. Sterile vaginal examinations were done on approximately 30 per cent of these patients, but in no instance was a serious attempt made to rupture the membranes or to carry out any vaginal procedure.

Because of considerable differences in type of patient, social level, and antenatal care, we have avoided detailed analyses of morbidity and incidence of complications other than placenta previa. No prolonged follow-up of either mother or baby was possible, and if both left the hospital alive and well, they were classified as such.

### Results

Each of the two groups contained fifty patients. They were stated to be similar only in that they had placenta previa. Table I shows that their ages were roughly comparable, and that the proportion of primiparas to multiparas was not too different: 20 and 27 per cent. It is of interest that the experimental group had almost twice as many previous babies as the control group. What cannot be shown are the differences in diet, antenatal care, and other advantages which accompany the great differences in social level.

TABLE I. COMPARATIVE STATISTICAL DATA OF THE EXPERIMENTAL AND CONTROL GROUPS

	NUMBER	AGE	PARITY	PRIMIP- ARAS	RACE		METHOD OF DELIVERY
		(YEARS)			WHITE	NEGRO	
Experimental	50	27.5	3.58	20%	40%	60%	Vaginal
Control	50	30.2	1.98	27%	100%	0	Cesarean section

The total number of living babies obtained by the two divergent methods of delivery is roughly the same in both groups: experimental, 62 per cent, and control group, 64 per cent. In Table II, fetuses are separated into weight groups. It is to be noted that in both the experimental and control groups, there are no living babies below 1,500 grams, irrespective of method of delivery. In the group weighing 1,500 to 2,500 grams, the figures are approximately identical; 50 per cent of the fetuses in both groups survived. When the weight of the baby exceeded 2,500 grams, over 80 per cent were living, again with no real difference in the group delivered by cesarean section. This table also brings out the interesting point that 20 per cent of the babies were hopelessly premature, while 50 per cent were at term, consequently were "good risk" babies.

TABLE II. NUMBERS AND PERCENTAGES OF LIVING BABIES WITH REFERENCE TO WEIGHT AND TYPE OF DELIVERY

	TOTAL BABIES		LESS THAN 1,500 GRAMS		1,500 TO 2,500 GRAMS		TERM	
	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT
<i>Experimental:</i>								
Living	31	62	0	0	6	12	25	50
Dead	19	38	9	18	6	12	4	8
<i>Control:</i>								
Living	32	64	0	0	5	10	27	54
Dead	18	36	8	16	6	12	4	8

Table III shows the type of procedures used in addition to rupture of the membranes. It is noted that in eight cases, not even rupture of the membranes was effected. In most of these individuals labor had progressed so far on admission to the hospital that delivery sufficed to cure the condition. A Willett clamp was applied to the scalp in four instances, and in nine instances version and extraction were resorted to. This latter procedure was utilized only on previable babies and fetuses of borderline viability, and only one living child was obtained.

TABLE III. PROCEDURES USED AS ADJUNCTS TO RUPTURE OF THE MEMBRANES IN THE EXPERIMENTAL GROUP

	NO INTERVENTION	RUPTURE OF MEMBRANES	WILLETT CLAMP	VERSION AND EXTRACTION	CESAREAN SECTION
Experimental	8	42	4	9	0
Control	0	0	0	0	50

The placenta was perforated five times, and in every instance the perforation was found to be on the margin of the placenta.

There were no maternal deaths. Only one uterus was ruptured, following a version and a mistake in judgment as to the size of the baby. It was followed by an immediate supracervical hysterectomy. This patient was discharged from the hospital on the eighth day without morbidity.

In the cesarean section group there was one death. It was caused by a generalized peritonitis. This infection was incurred in 1942, and only sulfonamides were used as antibacterial agents. It seems likely that this death would not have occurred at the present time.

### Discussion

The therapy of placenta previa has been debated since Paul Portal first described the clinical condition and recognized its significance.<sup>13</sup> It may be stated categorically that the inception of cesarean section as a method of therapy for the condition has decimated the maternal mortality and reduced the fetal mortality by 50 per cent. A study of the literary summary included in Table IV, however, shows no direct correlation between the percentage of cesarean sections performed for placenta previa and the fetal and maternal mortality, and it must be noted that hand in hand with this method of therapy have gone blood transfusions and antibacterial agents.

TABLE IV. COMPARATIVE ANALYSIS OF SOME PUBLISHED RESULTS, SHOWING THE LACK OF CONSISTENT IMPROVEMENT IN FETAL MORTALITY WITH VARYING PERCENTAGES OF PATIENTS BEING DELIVERED BY CESAREAN SECTION

AUTHOR	NUMBER OF CASES	GROSS FETAL MORTALITY (PER CENT)	GROSS MATERNAL MORTALITY (PER CENT)	SECTIONS (PER CENT)
Stratz	173	44	0.6	3.4
Brown	3,103	54.2	4.4	8.7
Berkeley	5,107	60	6.2	12.0
Williams	162	31	3	18
Aldridge (Sloane)	215	39.2	4.1	20
Seeley	250	34.6	2.8	23
McAfee	174	23.5	0.57	39
Campbell	325	31	0.6	44
Aldridge (Woman's)	185	40.1	5.9	44.9

Prematurity is the most frequent cause of fetal mortality in placenta previa, as it is of fetal mortality in general.<sup>14, 15</sup> To bring about any considerable reduction in fetal mortality, therefore, we must carry these patients, or as many as is feasible, from the previable and borderline viability stages to approximate term. We are immediately faced with two widely divergent schools of thought: (1) the school which categorically states that all patients with a diagnosis of placenta previa should be delivered immediately regardless of the size of the baby or the general physical conditions extant; and (2) the school which states that patients should be brought, under observation, as close to term as possible unless delivery is forced early by excessive bleeding or the onset of premature labor. Obviously, the fetal premature death rate cannot be reduced by following the first school of thought. It is still too early to tell whether the maternal mortality will be increased by the latter policy, although recent communications tend to belie that impression.

The question of method of delivery is also controversial and tends to be divided into three divergent lines of thought. The first group adheres to delivery of all patients with definite placenta previa by cesarean section when

spontaneous delivery is not imminent on admission to the hospital. Another group would reserve the section for those patients in whom simple rupture of the membranes does not suffice. A third school categorically delivers all patients with placenta previa by vagina.

With certain modifications, we belong to the second school of thought. We believe that cesarean section should be reserved for those cases in which the baby is definitely viable, where simple rupture of the membranes does not suffice. Since the fetal mortality rate is so high where the weight is 1,500 grams or less, section should rarely be resorted to, and it should be used with caution in cases where the baby is between 1,500 and 2,500 grams. Naturally it would seem poor economy from the point of view of the fetus to perforate a placenta, perform a version, or pull a foot down when the baby approximates term.

If optimal results are to be obtained by observation of previable fetuses until definite viability is reached, let us stress that certain criteria of care must be fulfilled. The blood supply must be unlimited and immediately available. A "shock team" must be present at all times with equipment and "know how" to run in huge quantities of blood in short intervals. Qualified obstetricians should be in charge and immediately available. The house staff should be able to give a constant and competent supervision at all times. Insurmountable difficulties should be recognized early in attempting vaginal delivery and the line of attack changed. A setup for abdominal delivery should be immediately available.

### Conclusions

A large percentage of patients with placenta previa can be delivered vaginally without undue risk to mother or baby.

Previable babies should rarely necessitate cesarean section for delivery because of placenta previa.

In properly equipped hospitals, borderline viability and previability of the fetus should be an indication for prolonged observation where excessive bleeding or premature labor do not make this impossible.

Further investigation of this problem would be profitable.

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## DECIDUOSIS OF THE CERVIX AND VAGINA SIMULATING CARCINOMA

BERNARD LAPAN, M.D., NEW YORK, N. Y.

*(From the Department of Gynecologic Pathology, Lebanon Hospital, and the Department of Obstetrics and Gynecology, Jewish Memorial Hospital)*

**P**ATHOLOGISTS usually think in terms of decidua as contrasted to pseudo-decidua, and of true decidua in normal sites as distinguished from ectopic decidua. At the onset of pregnancy, the stroma of the uterine endometrium shows a striking transformation into decidua, the result of a progressive change beyond the stage of premenstrual hyperplasia, with no sharp demarcation along the way. There have been described, in the absence of pregnancy, pseudo-decidual reactions in the uterus in which the cells closely resemble true decidua. Most interesting, however, is the fact that there can occur, under the stimulus of pregnancy, a transformation of apparently normal cells outside of the endometrium into decidual cells. Changes of this type, developing at a distance from the pregnancy itself, belong in the category of ectopic decidua.

Although it is generally known that decidual cells can appear in the cervix and the vagina during pregnancy, specific instances have not often been recorded. Much less common is the group of cases with which we are here concerned, namely those with decidual masses in the cervix and vagina which may, clinically and pathologically, very closely resemble a malignant tumor, thus leading to serious error by the clinician and confusion for the pathologist who is not aware of the etiology.

In 1906, Taussig<sup>1</sup> reviewed the previous literature and his personal observations on ectopic decidua. He listed 11 possible sites for its occurrence and reported an unusual case of tubal pregnancy with multiple ectopic decidua formation in a parovarian cyst, both tubes and ovaries, the peritoneum, and cervix. There was, however, no tumor formation in the cervix, and he stated that decidua could occur in the cervix distinct and apart from the placental site, contrary to previous belief.

A case of unusual decidual reaction in the cervix was recently described by Hennessy.<sup>2</sup> His patient, a gravida vi, para v, was four months pregnant when a small, bleeding, cervical new growth was discovered. Biopsy showed a marked decidual reaction. She was delivered by caesarean section at 38 weeks, with an uneventful postpartum course.

In a review of five cases of proliferative or papillary lesions of the cervix associated with pregnancy, Edmondson and his associates<sup>3</sup> described none which were decidual in character.

Fluhmann<sup>4</sup> studied eighty-nine cervical lesions in pregnancy, and of this large number none were decidual masses. However, he mentioned the possible formation of decidual islands in the cervix, stating that they were not as fully

developed as those seen in the endometrium. In discussing this paper, Brown<sup>5</sup> remarked that, during pregnancy, endometrial implants on the cervical and vaginal mucous membranes could bleed and present an appearance similar to that of carcinoma of the cervix. It is possible that he was referring to the same type of case which we will describe in this paper. If so, we are inclined to disagree with the interpretation that decidua forms in previous endometrial implants because of complete lack of evidence for such a view in our specimens.

We have encountered three cases, two in the cervix and one in the vaginal mucosa adjacent to the cervix, in which the formation of a tumor mass by decidua simulated malignant disease. They appear to represent a clinical entity which should be considered in the differential diagnosis of cervical and vaginal tumors occurring during pregnancy.

### Case Reports

CASE 1.—G. B., aged 33 years, a gravida i, para 0, appeared for examination by her physician in October, 1938, because of increasing vaginal bleeding. Past medical and surgical history was normal. Her previous menstrual history was not unusual, but her last period had occurred the previous June. Examination showed a uterus enlarged to the size of a three months' pregnancy, with a few hard, nodular masses in the anterior wall. There was profuse bleeding from the vagina, apparently from a soft, proliferating mass covering the entire cervix. The impression was that this was definitely a malignancy of the cervix and a biopsy was taken for confirmation.

The pathologist reported, "The sections reveal [Fig. 1] fragments of tissue in which numerous cervical glands are present. The entire stroma shows a very striking transformation into typical decidua of pregnancy. The impression here is that the stroma of the cervix has undergone decidual change in an ectopic site as a result of pregnancy. Diagnosis: Diffuse deciduosis of the cervix."

The pregnancy continued without further abnormality until one month before term, in February, 1939, when a vaginal examination again caused profuse bleeding. A normal spontaneous delivery occurred in March, 1939. A biopsy of the cervix (Fig. 2) was performed in June, 1939, on an area which appeared to be an erosion. The pathological report at that time was as follows:

"The cervix is diffusely permeated by glandular structures which are lined by a single layer of columnar cells of the mucous type, and there is papillary formation in some portions. As a result of this permeation, the cervix is seen to have a spongy structure. The decidual changes observed in the previous biopsy are no longer present. Diagnosis: Diffuse adenomatosis of the cervix."

The cervix was cauterized and healing took place normally. No further abnormality has since developed.

CASE 2.—A 35-year-old gravida ii, para i, three months pregnant, went to her local physician in July, 1946, for obstetrical care and was told, after examination, that she had a "cancer of the womb." Alarmed, she went to a second physician who found a large mass, smooth and apparently covered by vaginal mucosa, filling the posterior fornix of the vagina adjacent to, but not part of, the cervix. He corroborated the clinical diagnosis and referred the patient to a gynecologist, who also thought that the tumor was malignant but performed a biopsy.

The specimen showed (Fig. 3) a definite and marked decidual reaction in a mass of tissue surrounded by fibrous stroma and vaginal epithelium. The patient had an uneventful pregnancy and delivered spontaneously at term. Postpartum examination showed a normal cervix and no residual tumor mass or other lesions in the vagina.

CASE 3.—A. C., 31 years old, a gravida ii, para i, consulted her family physician in March, 1946, because of two weeks of amenorrhea. Her past medical and surgical history was normal. On routine examination, a large polypoid mass was found covering the external os. The possibility of malignancy was strongly considered and a biopsy was performed. The laboratory report was as follows:

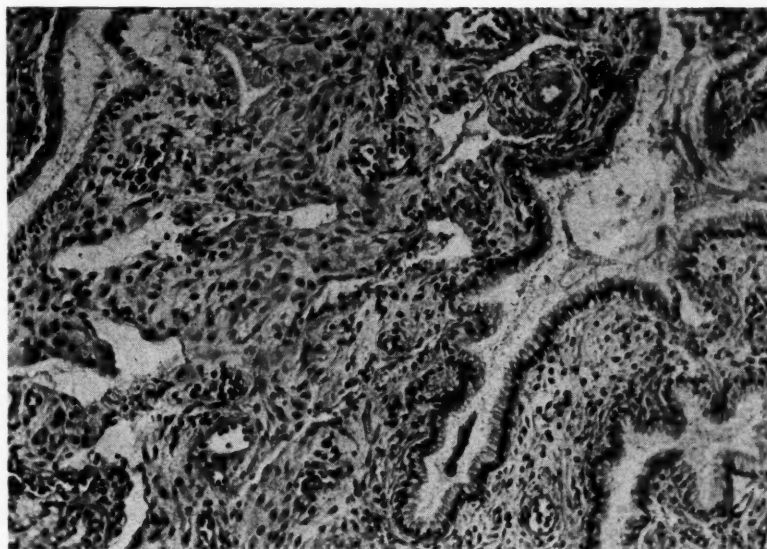


Fig. 1 (Case 1).—Biopsy of tumor mass of cervix. The cervical stroma cells show transformation into true decidua. ( $\times 100$ .)

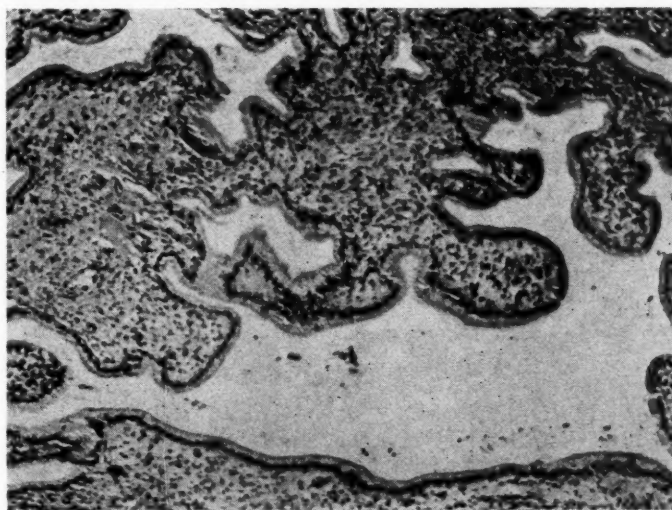


Fig. 2 (Case 1).—Cervical biopsy three months post partum. There is a normal stroma with increased numbers of cervical glands. ( $\times 100$ .)

"The specimen [Fig. 4] consists of several soft, pea-sized masses removed from the cervix. Microscopic examination shows fibrous stroma infiltrated by epithelial hyperplasia with some pearl formation. The cells are hyperchromatic and anaplastic. Diagnosis: Anaplastic carcinoma."

The patient was then referred to a gynecologist, who found the uterus enlarged and softened and made a diagnosis of pregnancy. With this information, the pathologist reviewed the slides and corrected the diagnosis to that of decidual reaction in the cervix. Another pathologist confirmed the latter opinion. Without further treatment, the patient delivered spontaneously at term and the cervix was found to be entirely normal on examination six weeks postpartum.

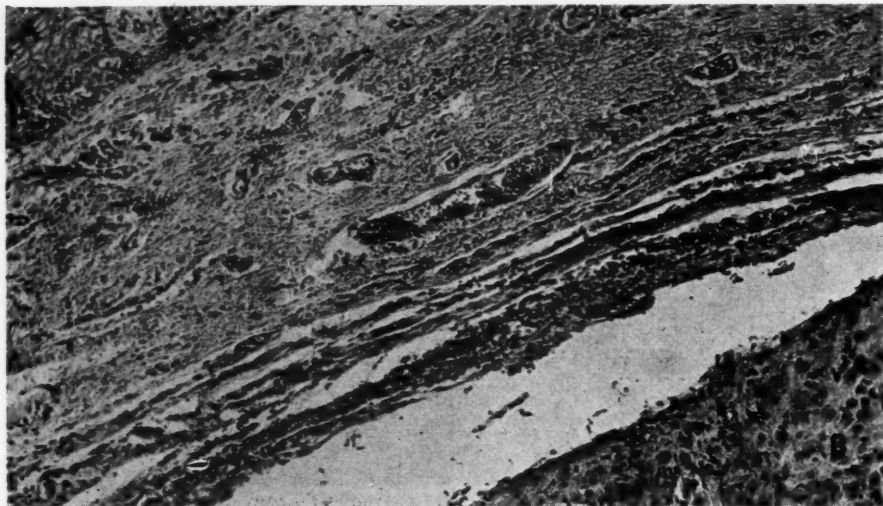


Fig. 3 (Case 2).—Biopsy of vaginal tumor mass. Vaginal mucosa, left upper corner (A). Decidual nodule, right lower corner (B). ( $\times 100$ .)

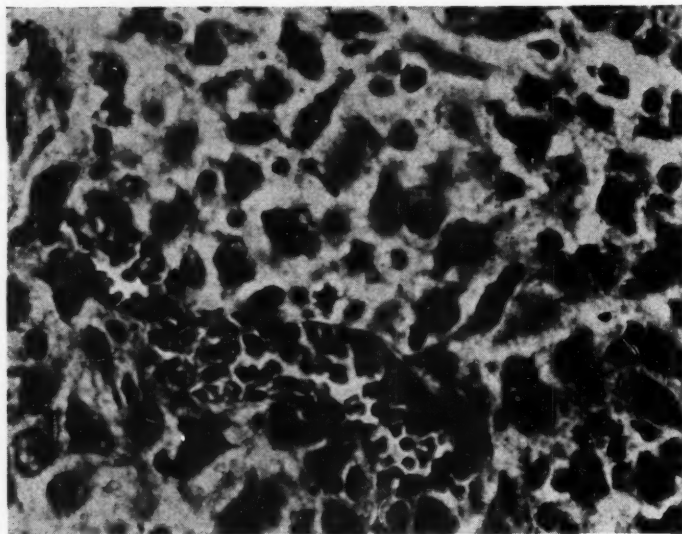


Fig. 4 (Case 3).—Biopsy of cervical tumor mass. The decidual cells resemble anaplastic carcinoma. ( $\times 500$ .)



### Discussion

These cases demonstrate that decidual masses or, as we prefer to designate the condition, deciduosis, may occur in the vagina or cervix in such a form that an erroneous clinical or pathological diagnosis of carcinoma can easily be made. For that reason, adequate biopsy and histologic study is essential.

It is apparent that conservative therapy is indicated in all of these cases, and that the outlook is good for normal delivery and complete regression of the tumor within a short period post partum. None of our patients had an associated placenta previa or low implantation of the placenta.

There was no evidence, in any of our cases, to indicate the presence of misplaced endometrial tissue or cells as the site of decidua formation. It is most likely, in our opinion, that the deciduosis arises in ectopic sites as a result of the inherent ability of certain cells to respond to the hormonal stimulus or biochemical changes of pregnancy. The mechanism of this alteration is, of course, unknown.

The differential diagnosis of deciduosis of the cervix and vagina as described here must include, besides carcinoma and other malignant tumors, decidual or placental polyps arising from the endometrial cavity and presenting through the external os of the cervix, as well as benign cervical adenomatous and epithelial polyps. Only by bearing all of the possibilities in mind can an accurate differentiation be made.

### Conclusions

1. Three cases of deciduosis of the cervix and vagina in pregnancy are described in which, clinically, the tumor appeared malignant.

2. Conservative therapy and normal delivery were carried out in all three instances, with complete regression post partum.

3. The condition develops as a form of ectopic decidua, without apparent evidence of pre-existing endometrial implants, and appears to comprise a definite clinical entity.

The author expresses his appreciation to Drs. H. Aranow, H. Gordon, S. B. Gelman, and A. I. Friedman for their aid in furnishing clinical data, and to Drs. J. C. Ehrlich and A. Schwarz for their cooperation in assembling the pathological material.

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## OCCURRENCE OF UTERINE FUNDUS CARCINOMA AFTER PROLONGED ESTROGEN THERAPY

A. VASS, M.D., SPRINGFIELD, ILL.

(From the Memorial Hospital)

IT HAS so far not been definitely proved whether or not the prolonged therapeutic use of estrogenic substances may result in the production of uterine carcinoma in the woman. Fremont-Smith, Meigs, Graham, and Gilbert,<sup>1</sup> in 1946, reported one case, in which adenocarcinoma of the uterine fundus occurred in a woman in the childbearing age. This patient received for the treatment of endometrial hypoplasia between May, 1937, and September, 1945, 392 Gm. of estradiol, 1,085 mg. of estrone sulfate, and 18 mg. of diethylstilbestrol. Uterine curettage in 1942 showed hyperplastic endometrium. Repeated uterine scrapings in 1945 revealed adenocarcinoma of the fundus. In the opinion of Meigs, et al., this carcinoma was directly caused by estrogen therapy.

Notwithstanding, Novak,<sup>2</sup> in 1947, believed that so far no case of human cancer has been recorded in which the evidence for an estrogenic causation is unimpeachable. However, in his opinion it is obvious that estrogen therapy should be held to a minimum or avoided altogether in patients who, because of heredity or through the existence of some other factor (not defined by Novak), may be considered to possess a predisposition to the disease. Novak assumed that the estrogenic factor is not the actual cause of cancer, but rather that the estrogenic stimulation, like any other irritation, is of importance only when superimposed on the still unknown genetic factor.

It is not intended to quote here the literature concerning experimental work on the same subject in animals. It seems to be quite clear, however, that experimental cancer production with estrogens in animals is possible. In view of this, and of the likelihood of an analogous course of events in human beings, it seems pertinent to report observations bearing on the problem. Two such cases will be reported here.

CASE 1.—A 50-year-old white woman was first seen in 1940. She had had irregular periods for the last two years and received medical treatment for hypothyroidism, obesity, and ovarian deficiency. For the last eighteen months she had received injections of Theelin twice a week, often as much as 100,000 units. Three months before, she had a single menstruation-like uterine bleeding, and some spotting since.

Diagnostic curettage on Jan. 13, 1940, resulted in the finding of originally atrophic endometrium with cystic hyperplasia (Fig. 1). The attending physician was verbally informed that the histological changes may be due to estrogen therapy, the discontinuance of which was advised.

However, due to the insistence of the patient, who was quite euphoric while receiving treatment, estrogen was again given in large amounts. During the years from 1937 to 1948, patient received approximately the following amounts of estrogenic substances: 15,000,000 units of Theelin, 600 mg. of Progynon, and 50 mg. of stilbestrol. This is only an estimate, as the patient was known to purchase Theelin without prescription when out of town. On May 20, 1948, she was subjected to another diagnostic curettage because of metrorrhagia. The pathological findings at this time were typical for a malignant adenoma of the fundus (Fig. 2). Subsequent hysterectomy confirmed this diagnosis.

Fig. 1.

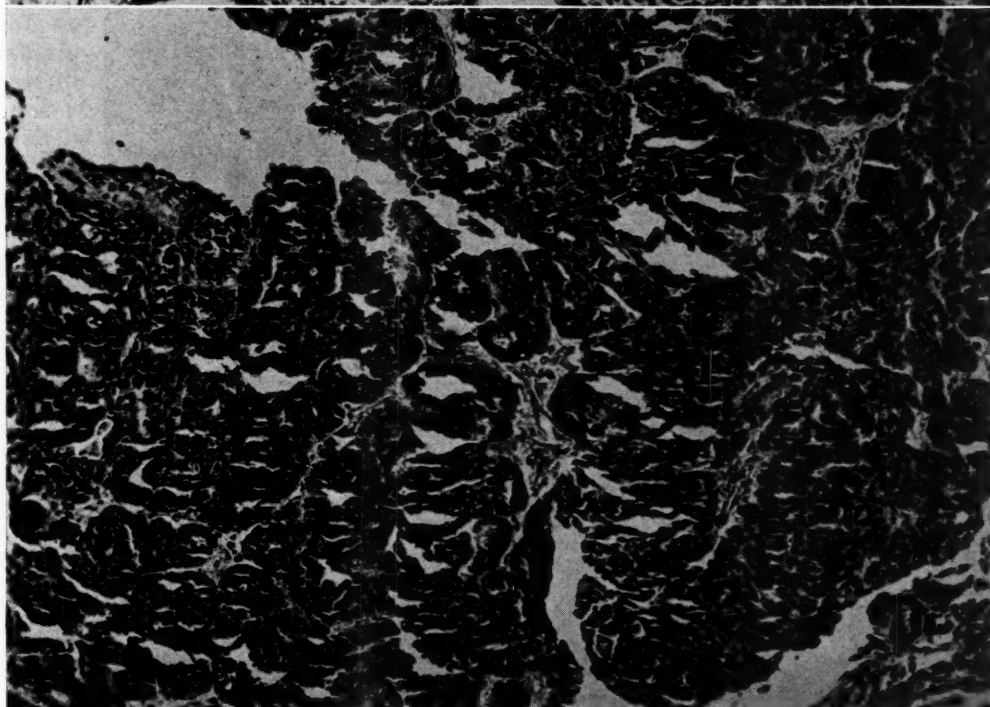
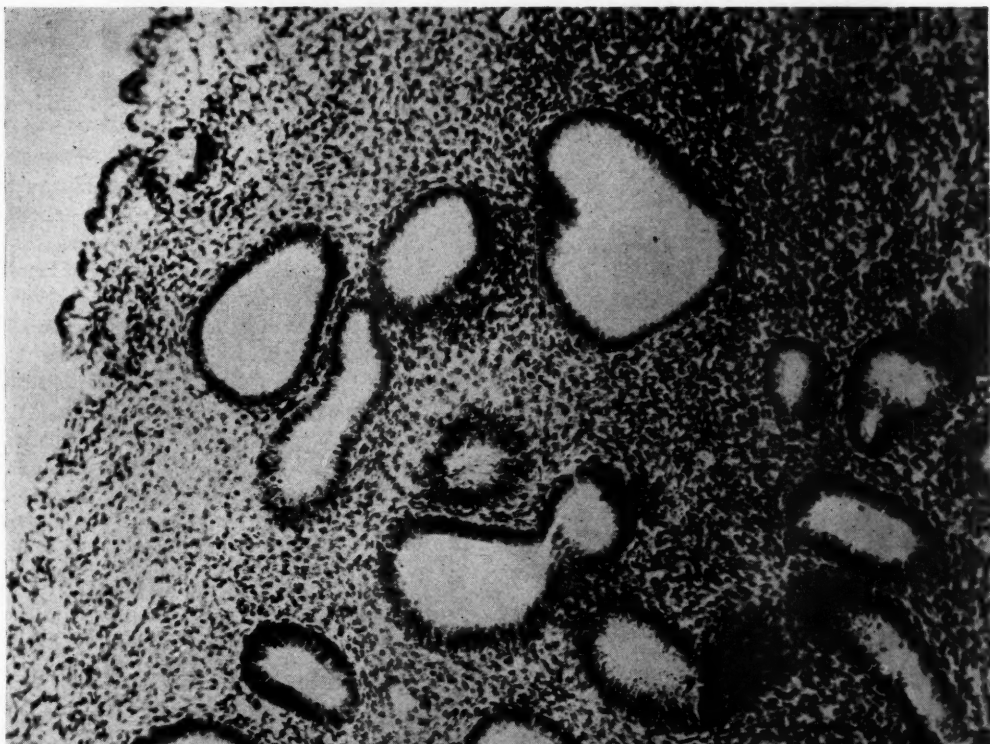


Fig. 2.

Fig. 1.—Cystic atrophy of endometrium with proliferating glandular epithelium. (Appr.  $\times 400$ .)

Fig. 2.—Malignant adenoma of uterine fundus after eleven years of estrogen therapy. (Appr.  $\times 400$ .)

Fig. 3.

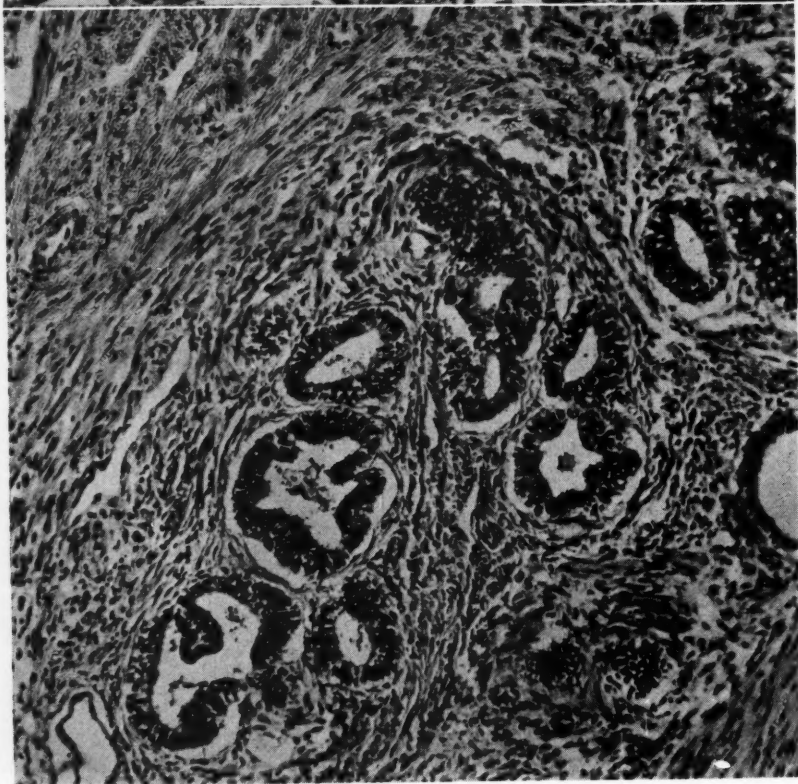
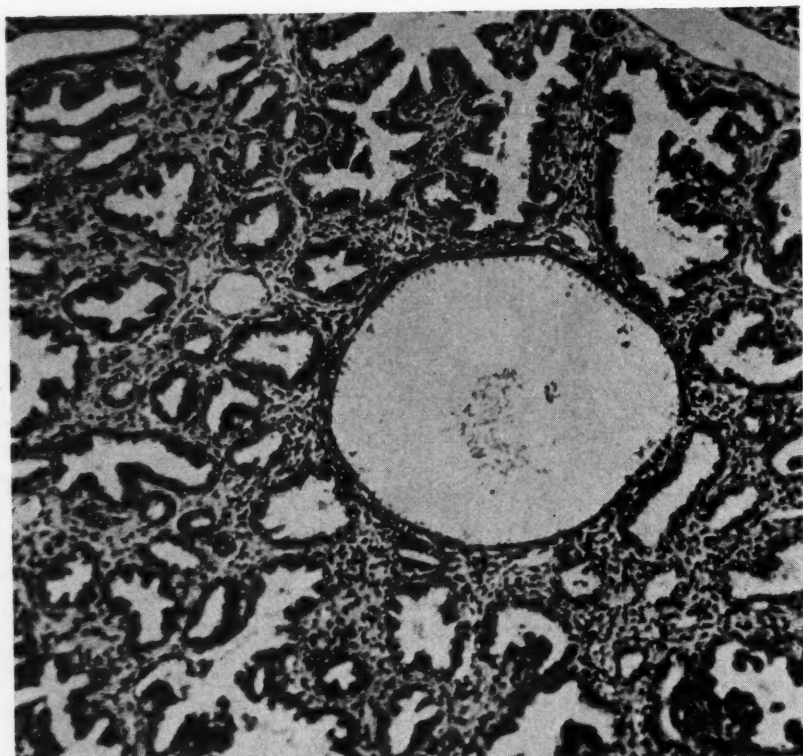


Fig. 4.

Fig. 3.—Superficial portions of adenocarcinoma of uterine fundus seen in curettements. (Appr.  $\times 400$ .)

Fig. 4.—Adenocarcinoma of uterine fundus invading muscularis. (Appr.  $\times 400$ .)



CASE 2.—A 35-year-old white woman was first seen on Feb. 27, 1947. She had been married for twelve years and was never pregnant, although she desired children. Her menstrual periods had always been irregular. For the last two years she had had menorrhagia. Several physicians, who saw her during this time, thought the condition to be menopausal. One physician, however, had told the patient two years before that she had an ovarian cyst. Nevertheless, she was given estrogen therapy. The amount and kind of hormones preoperatively used are not known. For the past two to three months the menorrhagia had increased and had been accompanied by pain in the left lower abdomen. Physical examination revealed a slightly enlarged uterus; a movable tumor mass was felt in the left adnexal region. A laparotomy on Feb. 28, 1947, revealed bilateral enlargement of the ovaries, which were removed. They measured 6 by 5 by 4 and  $5\frac{1}{2}$  by 4 by  $2\frac{1}{2}$  cm. On sections the usual number of follicular and corpus luteum cysts was present. However, the stroma was of a yellowish color and abundant. Microscopic examination revealed that the solid areas of both ovaries were occupied by theca cells. The pathologic diagnosis of theca-cell tumors of both ovaries was made. No uterine curettage was performed at this time. Subsequent to the bilateral oophorectomy estrogen therapy was instituted: 120,000 units of Theelin and 140 mg. of progesterone were given from March 2, 1947, to Oct. 17, 1947, at which date the patient was subjected to a diagnostic curettage because of recurring metrorrhagia. Microscopic examination of the uterine scrapings revealed a malignant adenoma of the fundus (Fig. 3). Total hysterectomy was performed on Jan. 13, 1948, and the diagnosis was confirmed. Invasive tendencies of the tumor into the muscularis were noted (Fig. 4).

### Discussion

In the first case a woman beyond the menopause received large amounts of estrogenic substances for approximately ten years. Histological and clinical evidence exists that after two years of this therapy the glandular epithelium of the uterine fundus showed proliferative tendencies. After ten years of therapy the proliferative tendency became uncontrolled. This sequence of events can be at best compared only with an uncontrolled experiment, but is nevertheless highly suggestive in view of the well-known effects of estrogenic substances on the uterine mucosa.

In the second case there is less suggestive evidence, as it is well known that theca-cell tumors or theca-cell hyperplasia of the ovaries often result in endometrial hyperplasia or malignant adenoma of the fundus. However, also in this case, the sequence of events is quite important, in view of the appearance of the fundus carcinoma several months after bilateral oophorectomy and "substitute" estrogen therapy.

In view of the moral and technical difficulties preventing us from obtaining more definite evidence of the role of estrogens in uterine carcinogenesis in human beings, such cases as these should nevertheless be regarded as a warning against the therapeutic use of estrogens in a promiscuous manner, at least until definite proof exists that they are not carcinogenic.

### Summary and Conclusion

Two cases of uterine fundus carcinoma occurring after prolonged administration of estrogens are reported. In both cases the sequence of events, together with the known properties of estrogens, strongly suggests an etiological relationship. For this reason it is believed that there should be no promiscuous therapeutic use of estrogens.

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## A BASIC ANALYSIS OF THE OBSTETRIC PELVIS BY ROENTGEN STUDY\*†

WILLIAM SNOW, M.D., NEW YORK CITY

**B**EFORE 1930, our knowledge of the maternal pelvis was based largely on study of the bones by anatomists and anthropologists, and by direct examination of the patient by the obstetrician. In 1932, Caldwell and Moloy<sup>1, 2</sup> devised a classification of the pelvis in which correlation of this older knowledge with roentgen study of the living was attempted. They followed this with a series of studies in collaboration with Swenson and also with D'Esopo.<sup>3, 4</sup> Due credit was given to previous workers such as DeWess (1826), Murphy (1846), Stein (1844), Weber (1830), and Turner (1885). In the early studies the previous workers had recognized more or less the same variations that were later visualized on roentgen study. Caldwell and Moloy gave new impetus to this important problem because by them roentgen study could readily be performed in a large series of cases, and because the findings when taken together with roentgen pelvimetry and the other obstetrical data are of real practical value.

They divided the pelvis into anthropoid, gynecoid, platypelloid, android, and asymmetric types. They also recognized that there occurs an overlapping of these types. I shall not attempt to describe these in detail. Instead, I shall present my own findings in the analysis of over 10,000 roentgen studies of pregnancy and bring out fundamental principles and a simplified approach.

In rendering a written description of the pelvis I have found that I could not adequately describe the various parts by following the terminology of Caldwell and Moloy. The types overlap to a marked degree and the extent of type varies. If the pelvic inlet were described as moderately android in the posterior segment and gynecoid in the anterior segment, I found that few would have a clear picture. However, when I began to classify the various parts of the pelvis in simple geometric terms, giving the degree, the reports were readily understood. The practical significance of these shapes may be easily recognized although the etiology is not clearly understood.

*Inlet.*—In trying to describe the pelvic inlet in geometric terms I found that the outline of the posterior segment is either trilateral or rounded in varying degree, and that the outline of the anterior segment is either rounded or wedged in varying degree. Roentgen study of the pelvis in 50 males shows that for the posterior segment, trilateral shape has an incidence of 86 per cent and for the anterior segment, wedged shaped is 84 per cent. (Table I). Analysis of 1,000 consecutive female roentgen pelvimetries shows rounded anterior and posterior segments in 80 per cent and wedged anterior plus trilateral posterior segment in 20 per cent. Therefore, it is safe to assume that the trilateral shape and wedging are male characteristics and that rounding is a female characteristic (Table II).

\*Most of the material was obtained from Harlem Hospital Obstetric Service, Bronx Hospital Obstetric Service, and from the Radiology Departments of the Bronx and Harlem Hospitals.  
†Presented June 9, 1948, at the Annual Meeting of the American Medical Association, Chicago, Ill.

TABLE I. MALE PELVIS. (50 CASES)

Inlet.—		Posterior Segment.—		Anterior Segment.—	
A. P. View		Trilateral, Rounded,	86 per cent 14 per cent	Wedged, Rounded,	84 per cent 16 per cent
Spines.—	Large,	70 per cent	Medium, 22 per cent	Small,	8 per cent
A. P. View					
Lateral Walls.—	Funnel,	68 per cent	Moderate 24 per cent conver- gence,	Slight con- vergence,	8 per cent
A. P. View					
Subpubic Notch.—	Very small,	36 per cent	Small, 60 per cent	Medium,	4 per cent
A. P. View					
Sacrum.—	Curved,	24 per cent	Shallow, 60 per cent Ridged, 10 per cent	Convex,	16 per cent
Lateral View					

TABLE II. TYPICAL GYNECOID PELVIS. INCIDENCE OF 306 OUT OF 1,000 CASES  
(30 PER CENT)

Inlet	Posterior segment, rounded
A. P. View	Anterior segment, rounded
Sacrum	Curved
Lateral View	
Spines	Small
A. P. View	
Lateral walls	Moderate convergence
A. P. View	
Subpubic notch	Large
A. P. View	
Sacrosciatic notch	Large
Lateral View	
Acetabular bulge	None
A. P. View	

In order to retain common terminology the fully female type inlet may be designated as gynecoid and the male type as android. The deeply rounded anterior and posterior segments of the inlet with deep anteroposterior diameter and narrow transverse diameter were designated as anthropoid by Caldwell and Moloy. According to the classification given here this may be safely grouped with the gynecoid, providing pelvic measurements are added.

The platypelloid pelvis of Caldwell and Moloy is characterized by rounded anterior and posterior segments of the inlet with a very low Turner Index, that is, a shallow pelvis with a relatively small true conjugate. I prefer to class this also as gynecoid and depend upon the pelvic measurements for further clarification. The shallow inlet in my experience appears to be due to poor bone nutrition as described elsewhere in this paper (Fig. 1).

**Sacrum.**—In the female, on the lateral roentgen view, the sacrum is curved in 45 per cent of cases, shallow in 30 per cent, and flat to convex in 25 per cent. In males the incidence is: curved, 24 per cent, shallow, 60 per cent, and convex, 16 per cent.

It would appear that shallowness indicates a tendency toward the male quality. However, shallowness may be akin to flatness or convexity, which are apparently due to deficient bone nutrition. In marked cases the upper portion of the sacrum is flat to convex and the promontory dips forward. The lower portion of the sacrum dips backward and may be sharply curved forward.

There are probably other causes, besides rickets, of disturbed bone nutrition which affect the sacrum. In 1939, Greulich, Thoms, and Twaddle<sup>5, 6</sup> showed that white female children have a high Turner Index (true conjugate divided by transverse of inlet). Later in life this index becomes reduced in some women,

which means that the anteroposterior diameter of the inlet tends to become shortened. Poor metabolism of estrogen<sup>7, 8, 9</sup> with high blood level due to vitamin B and liver deficiency might be a factor. Excessive estrogen causes bone demineralization in rats. In human beings, excess estrogen as in famine conditions causes osteomalacia with bone softening resembling parathyroid overactivity. This is not to be confused with the generalized osteoporosis following menopause where loss of estrogen eventually causes overactivity of the adrenals leading to a negative nitrogen balance. Severe starvation causes osteomalacia during puberty and pregnancy. Lack of protein in the diet may contribute to poor bone nutrition, since a negative nitrogen balance eventually evidences bone demineralization. The changes of the sacrum and pelvis may, therefore, be considered to be due to a mild form of osteomalacia. In male pelvimetry studies that I have done, the Turner Index tends to be higher than in females, indicating better bone nutrition on a hormonal basis. Testosterone favors strengthening of bone, probably by favoring a positive nitrogen balance.

The sacrum may be short or long depending on the number of spinal segments that are sacralized. Since this is developmental, determined during fetal life, and, since Warkany<sup>10</sup> has produced bone malformations in rats by causing vitamin B deficiency, it is possible that a causal relation exists and that future generations may not present this sacral variation (Fig. 1).

These suggested etiologies of variations of the pelvic architecture, (1) hormonal, (2) developmental, and (3) nutritional, are appealing because they offer a basis for possible control in future generations.

*Ischial Spines.*—In males the spines are large in 70 per cent, medium in 22 per cent, and small in 8 per cent. It is safe to assume that large spines in the female pelvis are indicative of malelike quality.

*Lateral Wall Convergence.*—In males the lateral walls are funnel in 68 per cent, moderately convergent in 24 per cent, and slightly convergent in 8 per cent. In females funnel shape occurs in only 10 per cent, moderate convergence in 40 per cent, and slight in 50 per cent (Fig. 1).

*Subpubic Notch.*—The subpubic notch in males is small in 96 per cent of cases and in females in 25 per cent. In males it is medium in 4 per cent and in females in 35 per cent. In males I have found no large subpubic notches and in females the incidence is 40 per cent (Fig. 1).

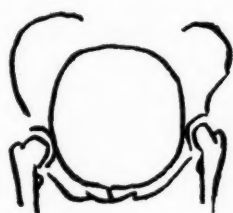
TABLE III. TYPICAL ANDROID PELVIS. INCIDENCE 114 OUT OF 1,000 (12 PER CENT)

Inlet	Anterior segment, wedged
A. P. View	Posterior segment, trilateral
Sacrum	Shallow or rounded
Lateral View	
Spines	Large
A. P. View	
Lateral walls	Funnel
A. P. View	
Subpubic notch	Small
A. P. View	
Sacrosciatic notch	Small
Lateral View	
Acetabular bulge	Seen occasionally
A. P. View	

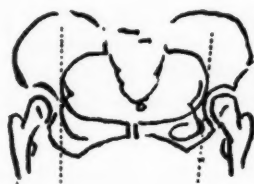
As stated previously, for the sake of greater accuracy, out of the total 10,000 cases, I made a statistical review of 1,000 consecutive roentgen studies of the female pelvis, made during late pregnancy. I was able to find what I considered to be a pure female pelvis in 30 per cent of cases, as outlined in Table II. Likewise I was able to find a pure android pelvis in 12 per cent of cases



9.



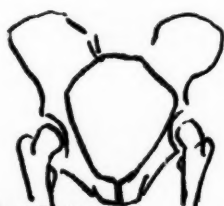
GYNECOID:  
Inlet  
Post. seg.--round  
Ant. seg.--round



GYNECOID:  
Lat. walls--slight or moderate, convergence  
Spines--small  
Subpubic notch--large



GYNECOID:  
Sacrum---curved  
Sacro-sciatic notch--large



ANDROID:  
Inlet  
Post. seg--trilateral  
Ant. seg--wedged



ANDROID:  
Lat. walls--funnel  
Spines-----large  
Subpubic notch--small



ANDROID:  
Sacrum----shallow  
Sacro-sciatic notch--narrow



POOR BONE NUTRITION  
AS RICKETS:  
Moderate



AS RICKETS:  
Marked



AS RICKETS:  
Severe



SACRUM:  
Short



SACRUM:  
Double promontory



SACRUM:  
Long

Fig. 1.

as outlined in Table III. It is important to recognize that 58 per cent of cases showed a mixture or overlapping of the two types in varying degree as shown in Table IV. It has, therefore, proved simplest to describe each factor of the pelvis independently using geometric terms as shown in Table V. Asymmetry of the pelvis is rare and is usually caused by old fracture, bone infection of the hips, extreme scoliosis, or poliomyelitis.

TABLE IV. MIXED PELVES (ANDROID AND GYNECOID). INCIDENCE 580 OUT OF 1,000 CASES (58 PER CENT)

Inlet A. P. View	Pure, 43 per cent. (Anterior and posterior segment rounded or anterior segment wedged with posterior segment trilateral.)  Mixed, 57 per cent. (Anterior segment rounded with posterior trilateral or anterior segment wedged with posterior rounded.)
Spines A. P. View	Small, 56 per cent, Medium, 20 per cent, Large, 24 per cent.
Lateral walls Convergence A. P. View	Slight, 62 per cent, Moderate, 22 per cent, Marked, 16 per cent.
Subpubic Notch A. P. View	Wide, 22 per cent, Medium, 22 per cent, Small, 56 per cent.

TABLE V. PELVIC ARCHITECTURE

Inlet A. P. View	Anterior segment rounded (gynecoid) slight, moderate, deep wedged (android) slight, moderate, marked  Posterior segment round (gynecoid) slight, moderate, marked trilateral (android) slight, moderate, marked
Sacrum Lateral View	Curved (gynecoid) Shallow (android) Flat to convex upper portion Lower part of sacrum forced back and coccyx angulated forward (poor bone nutrition) Ridged (android)
Ischial spines A. P. View	Small (gynecoid) Large (android)
Convergence lateral walls A. P. View	Straight, slight, moderate (gynecoid) Funnel (android)
Subpubic notch A. P. View	Large (gynecoid) Small (android)
Bulge acetabulum A. P. View	None (gynecoid) Present in males about 10 per cent
Pubic lips A. P. View	Small and light (gynecoid) Large and heavy (android)
Sacrosciatic notch Lateral View	Wide (gynecoid) Narrow (android) Wide in lower part associated with back sweep of sacrum (poor bone nutrition)

In order to bring out the relative value of roentgen analysis of the pelvic architecture a brief outline of some of the causes of dystocia follows:

CAUSES OF DIFFICULT ENGAGEMENT

1. Poor shape of inlet:
  - (a) posterior segment trilateral (android)
  - (b) anterior segment wedged (android)
  - (c) posterior segment of inlet flattened (poor bone nutrition, usually seen with flat to convex sacrum)
  - (d) asymmetry (rare)
2. Small measurements of inlet (common)
3. High, double, or forward promontory (poor bone nutrition and/or developmental, occasional)
4. Soft part interference: pendulous uterus, full bladder or rectum, polyhydramnios, fibroids, ovarian cyst, placenta previa, abdominal pregnancy, short cord, or cord twisted about fetus
5. Fetal head, too large, too firm, malformed
6. Malpresentation (usually associated with above factors)

DIFFICULTIES AT THE MIDPELVIS

1. Sacrum, shallow, ridged (android)  
flat or convex (nutritional)
2. Ischial spines, large (associated with small interspinous measurements, android)
3. Funnel lateral walls (android)
4. Poor flexibility of tissues (elderly primipara, defective nutrition)
5. Small pelvic measurements (common)
6. Fetal head, too large, too firm, malformed

Summary

In review, it would seem that the important basic influences on the pelvis are:

1. Hormonal, resulting in gynecoid (female), android (male), and mixed types.
2. Developmental, which influence on the pelvis is recognized largely at the present in the degree of sacralization of the sacrum.
3. Nutritional, commonly rickets. Also, vitamin B deficiency may cause excess accumulation of estrogen by deficient liver function, leading to calcium mobilization and weakening of bones.
4. Injury or infection, as with osteomyelitis. This may cause asymmetry of the pelvis, an uncommon finding.

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## THE PATTERN OF UTERINE GROWTH DURING PREGNANCY IN MONKEYS AS SHOWN IN AN X-RAY STUDY\*

EDWARD CLARK GILLESPIE, M.D.,† ELIZABETH MAPELSDEN RAMSEY, M.D., AND  
SAMUEL R. M. REYNOLDS, PH.D., BALTIMORE, MD.

(From the Department of Embryology, Carnegie Institution of Washington)

CONSIDERABLE interest has been evidenced in recent years by gynecic physiologists and by clinicians in growth patterns of the gravid uterus.<sup>1-10</sup> Observations by one of us,<sup>3-6</sup> chiefly upon the rabbit, led to a new impression concerning uterine accommodation of the products of conception. Briefly stated, these observations support the belief that there are, in litter-bearing animals, three distinct periods of uterine growth during gestation. These are, namely:

a. *Preparation*.—This consists of proliferation of endometrium and myometrium under the influence of progesterone and it diminishes about the time of nidation.

b. *Hypertrophy and Hyperplasia*.—Increasing intrauterine tension due to the enlarging fetus constitutes a growth stimulus by which all uterine elements grow.<sup>11</sup> The general shape of the conceptus sites in this stage is spherical. Tension within the uterus mounts rapidly due to hydrostatic forces cited elsewhere and beyond a certain point this tension has a deleterious effect causing reduced blood-flow through the uterus<sup>5</sup> and ischemia of the myometrium.<sup>3</sup> The degree of circulatory impairment to the uterus increases as growth in the spherical form continues and a critical point is reached.

c. *Elongation*.—The critical phase described above is relieved abruptly by a physiological mechanism which has been termed conversion. The essence of conversion is that the conceptus sites rapidly elongate into a cylindrical shape, thereby reducing the intrauterine tension. This is attributable to forces operating in accordance with established hydrostatic principles.<sup>4</sup> Blood-flow through the myometrium thereafter is again rapid. Since tension served as the stimulus for uterine growth, it is obvious that the diminution of tension associated with the change of shape removes to a large degree this stimulus. Therefore, enlargement of the cylindrical uterus is accomplished by stretching of myometrial elements already present with minimal growth of new tissue. Consequently, this period comes to a self-limiting end under normal conditions, when stretch limits are approached. The fetus grows rapidly in the tubular uterus and it seems possible that the maturity of a given species at birth is directly proportional to the relative amount of its gestational period that is spent in a converted uterus.

These findings are rather well documented in litter-bearing animals<sup>12</sup> and will not be further elaborated upon here. The purpose of this paper is to ana-

\*Read by invitation, before the Baltimore Obstetrical and Gynecological Society, Feb. 11, 1949.

†Carnegie Fellow.



lyze data concerning the growth patterns in the primate uterus in order to ascertain to what extent conditions similar to those prevailing in the uterus duplex of the rabbit pertain to the uterus simplex.

### Methods and Materials

The investigation was in two separate phases consisting of: a. an analysis of soft tissue x-ray outlines of pregnant monkey uteri, and b. weighing fixed specimens of fetuses and uteri at various gestational ages.

a. In the x-ray study six pregnant rhesus monkeys (*Macaca mulatta*) were used. Of these, two aborted and one was sacrificed on the ninetieth gestational day for other purposes of the study. Each animal was subjected to laparotomy early in pregnancy (between the thirty-sixth and sixty-eighth days) at which time radiopaque substances (silver sequins and silver wire) were sewn at predetermined points to the gravid uterus. At the same time a metal clip was fastened to the posterior lip of the cervix. It was following these procedures that two of the animals aborted. The remaining four were subjected to soft tissue x-rays of the abdomen, both anteroposterior and lateral views obtained. X-rays were taken at frequent intervals throughout the remainder of these pregnancies. It was soon found that for purposes of outlining the uterus, the anteroposterior views were of limited assistance. Further, the radiopaque markers shifted greatly in position as growth continued and they could not be used as guides in reading x-rays. Consequently, the results are based on lateral views of the uterus without the use of markers.

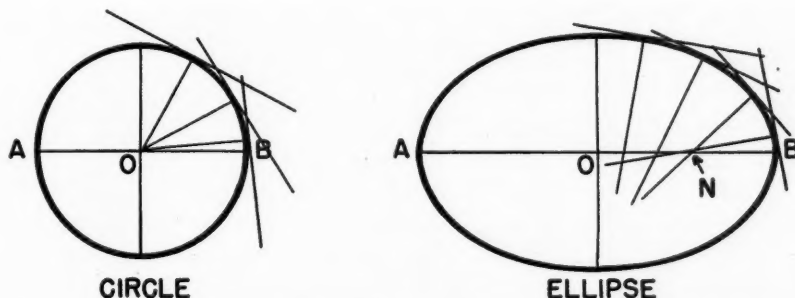


Fig. 1.—Method used in obtaining projection ratio ( $ON/OB$ ) in the analysis of various curves. The line  $AB$  representing greatest length is bisected at  $O$ , the perpendicular extended from  $O$  ( $CD$ ) dividing the figure into four quadrants. Tangents are drawn to curves of the two upper quadrants and perpendiculars from these are extended till they cut  $OB$ . The outermost tangent cut is called  $N$  and the ratio  $ON/OB$  approaches 1 as the organ increases in cylindrical shape. In the circle,  $ON/OB = 0.25$  or  $0$ , whereas, in the ellipse shown,  $ON/OB = 22:42$ .

In each series the x-rays were placed on a horizontal viewing box and the outline of the uterus was accurately transferred to paper by means of a suspended precision pantograph. The curves of the lower quadrants were difficult to visualize in many instances but were not important in the calculations. The drawings were analyzed as indicated in Fig. 1 which shows the principle applied to a circle and an ellipse, respectively. A line was drawn joining the highest point of the fundus to the cervix.  $AB$  was bisected and a perpendicular erected ( $CD$ ) which divided the uterus into four quadrants, of which the posterior and anterior upper ones were used. Tangents were drawn to the curvatures of these quadrants and perpendiculars erected to the tangents. The perpendiculars were extended till they cut the line  $AOB$  and the outermost perpendicular cuts  $AOB$  at  $N$ . It is obvious that if the uterus were a perfect

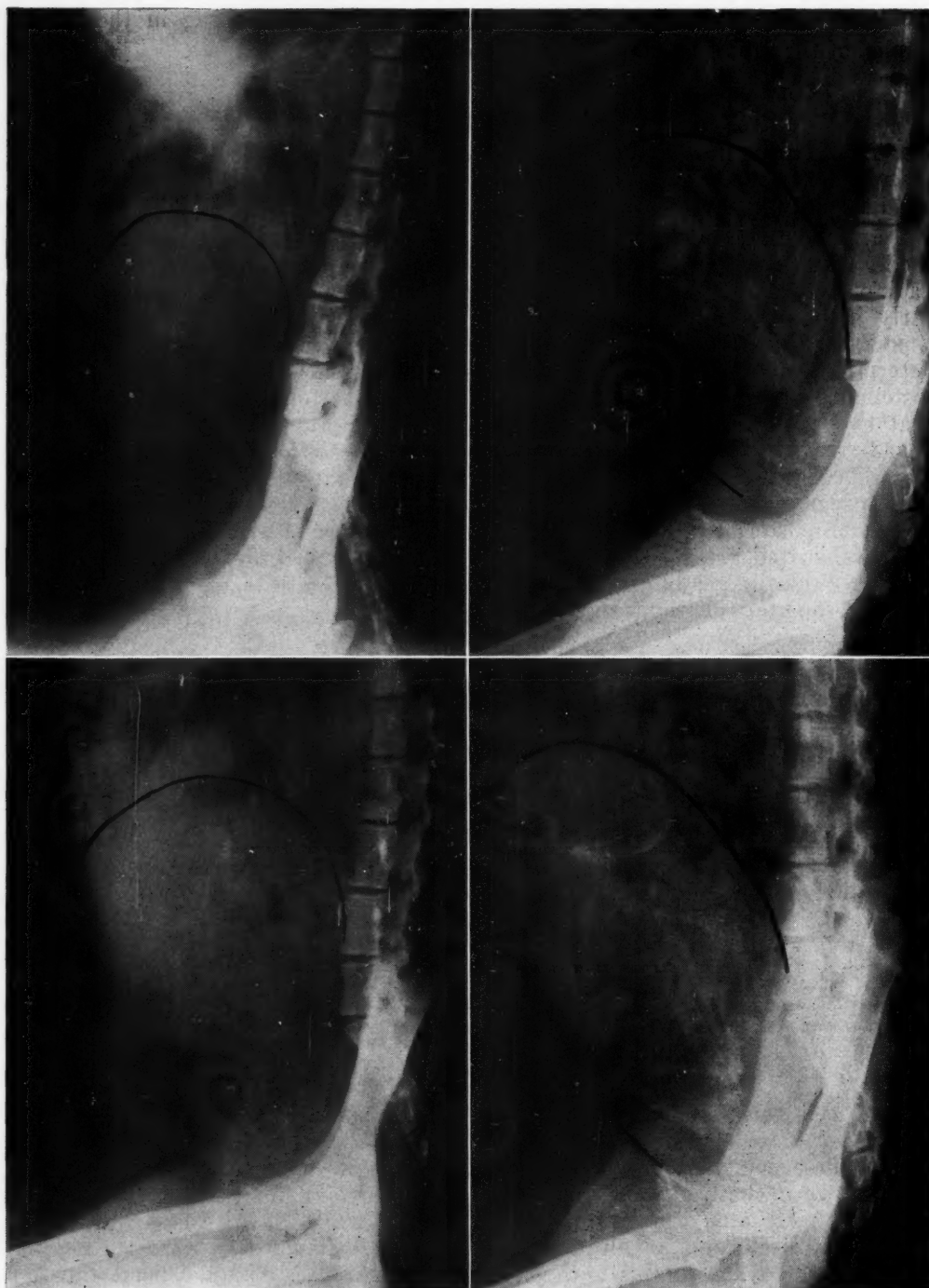


Fig. 2.—Lateral soft tissue x-rays of uteri at progressive intervals through gestational period. The general appearance before the 100th day is spherical and thereafter becomes cylindrical. The radiopaque markers are visible in some plates. It has been necessary to ink in outlines because of loss of contrast in photography and reduction. Upper left, 59 days, upper right, 78 days, lower left, 99 days, lower right 104 days.

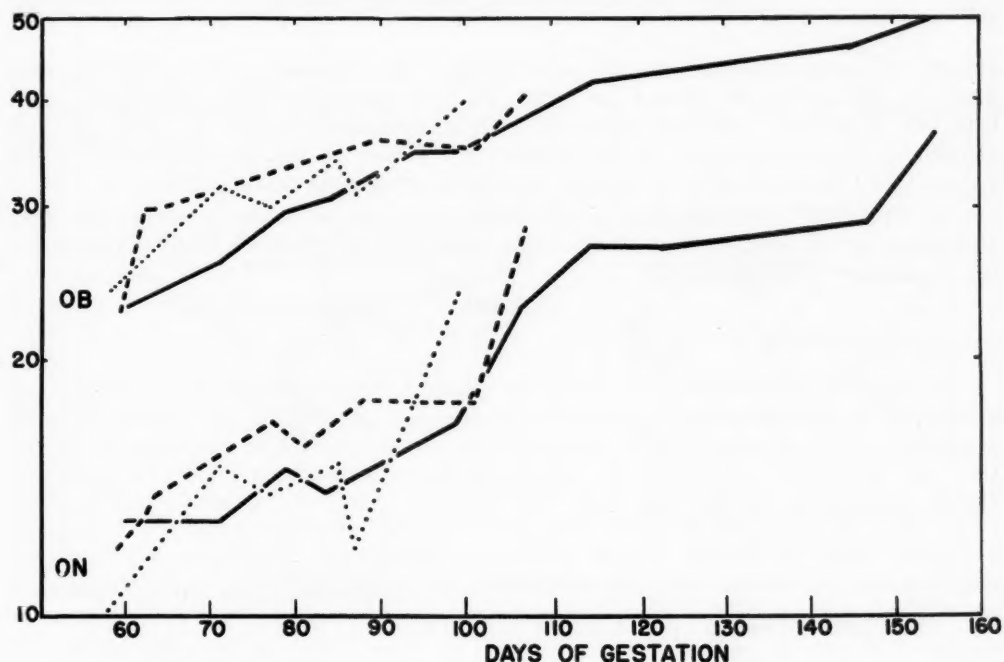


Fig. 3.—Logarithm graph representing curvature of anterior upper quadrant. As the lower line (ON) approaches the upper (OB) the uterus is becoming cylindrical. Note that in all specimens there is a sharp upward curve around the 100th day.

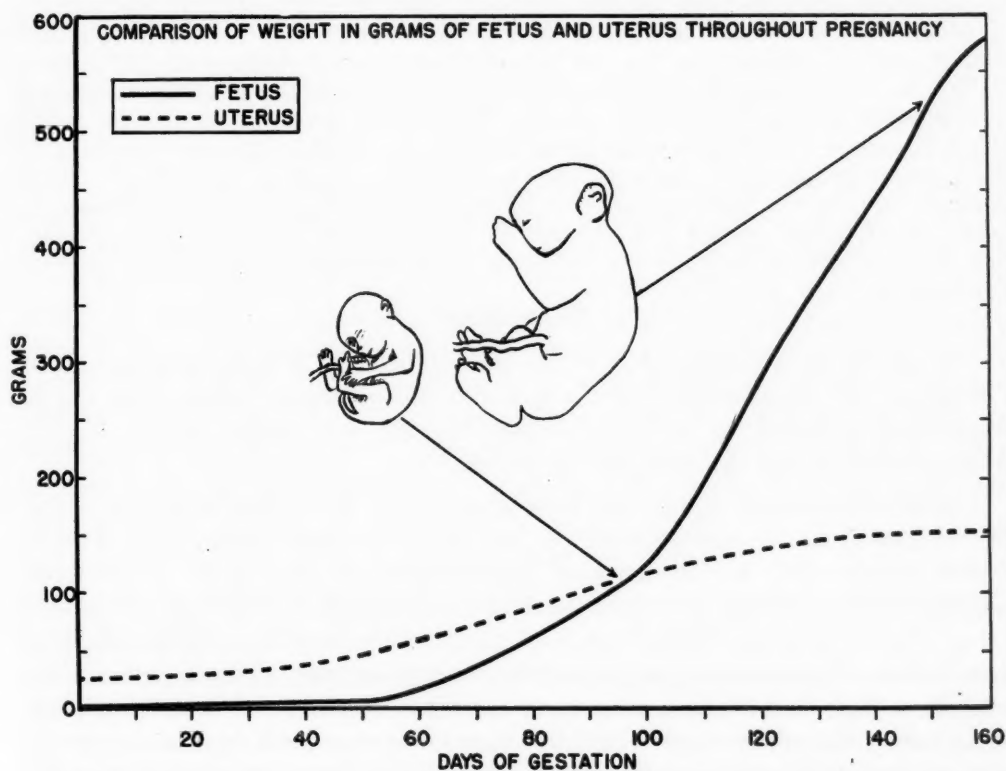


Fig. 4.—Fetal and uterine weight gain throughout pregnancy. Following the 100th day the curve of uterine weight gain levels off while that of fetal gain climbs rapidly. This illustrates the importance of the conversion period in maturation of the fetus. It further adds support to the belief that following conversion uterine enlargement is due to stretching rather than to growth of new tissue.

sphere, all perpendiculars would pass through O. The value ON would be zero, and the ratio ON:OB would be zero. As the uterus becomes cylindrical, the line ON lengthens and the value ON:OB approaches 1:1 or 1. This method eliminates changes in size of the uterus as a factor in the determination. The values ON:OB were plotted on semilogarithm graphs as actual ratios.

b. Specimens consisting of fixed monkey fetuses at various gestational ages and their uteri, empty of contents, were carefully weighed and allowance made for fixation.

## Results

### *X-ray Studies.—*

a. Superficial scanning of the x-ray plates (Fig. 2) suggests strongly that a change in uterine shape has occurred between the 100th and 105th days of gestation. This observation is more obvious when a series of pantograph transfers are examined. Finally, in removing the observations from the realm of visual judgment to that of logarithm graphs, the results are equally clear (Fig. 3). The graphs indicate that on or shortly after the 100th day there is a fairly rapid elongation of the uterus as it tends to approach a cylindrical shape which it retains for the remainder of gestation. The exact length of time it takes to complete this process cannot be determined from these observations except to say it is less than five days. Conversion occurs rapidly in the rabbit, i.e., in about two hours but is probably somewhat longer in primate uteri.

b. In Fig. 4 is plotted the gain in weight of fetus and uterus throughout gestation of the monkey. The figures were obtained as mentioned previously by weighing material from the Carnegie collection and they follow the pattern of other observers inasmuch as is possible to demonstrate.<sup>14</sup> It will be noted that the curve representing uterine weight flattens out following the 100th day. This is to be expected if growth has diminished and actual stretching instituted as suggested by the x-ray study above. Further, it can be seen that the fetus about the same time begins to increase in absolute weight rapidly, regardless of the percentile increment gain which is, naturally, always decreasing.<sup>15</sup> This marked increase in absolute weight following conversion has been shown to hold true in other species and is believed due to an interaction of several factors, not the least of which is the reduction of intrauterine tension and improved circulation.

## Discussion

From the data presented it seems possible that at a uniform time and in a relatively short period of time the gravid monkey uterus changes from a predominantly spheroid to a predominantly cylindrical organ. What further evidence is there that this actually takes place?

Studies have been carried out in monkeys which show that before the 100th day of gestation, the endo-myometrial arteries proliferate greatly and become closely coiled. This is demonstrated diagrammatically in Fig. 5. The coiling appears to be in excess of current demands of the organ. Following conversion (at or shortly after the 100th day) an abrupt transition of this vascular pattern supervenes. This consists of rapid uncoiling along the whole length of the arteries so that they become completely straight except for an occasional right angle turn. Obviously some event has taken place which has made these vessels pay out and it is apparent that the coiling had been in preparation for this event. These observations, made prior to the investigations into changing



patterns of uterine growth, were enigmatical until the concept of rapid uterine elongation following conversion was elaborated on the basis of observations upon the rabbit.

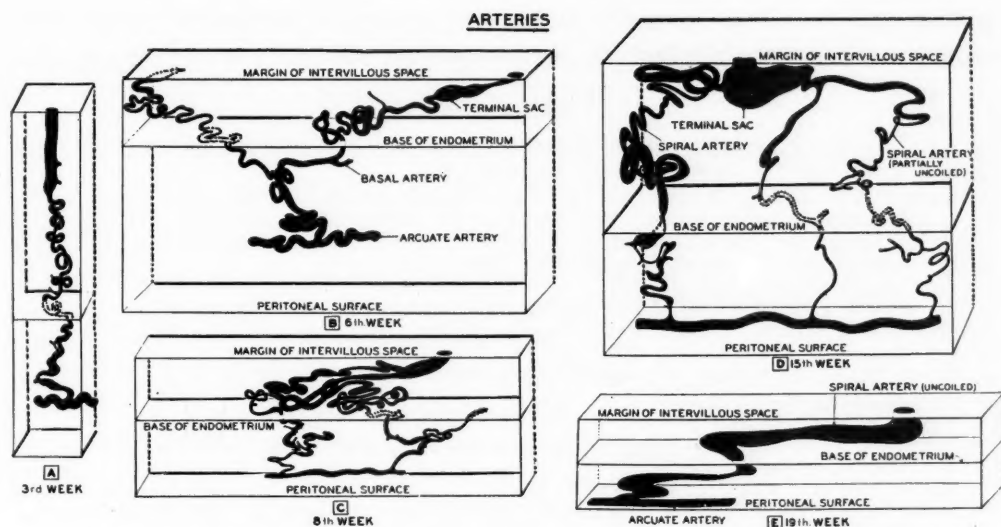


Fig. 5.—A composite diagram made from serial sections of the pregnant monkey uterus at various intervals during gestation. Note that following the 100th day the vessels of myometrium and endometrium which were previously coiled have become straightened and elongated. All sections taken at placental site (From Ramsey.<sup>13</sup>)

The foregoing résumé correlates several separate observations. It supports the view that, in the process of uterine accommodation of the conceptus, several distinguishable physiological states exist, following in order. It implies that after conversion, uterine growth diminishes greatly and stretching begins, thereby possibly influencing the length of gestation. Further, it shows that absolute fetal growth is much greater following conversion, which means the fetus matures rapidly in this period. It is most important in terms of fetal maturity, then, that no interruption or shortening of the postconversion phase takes place. The growth of a normal amount of uterine wall with normal vessels prior to conversion would seem to be important in assuring a normal postconversional period. This, and other methods of studying conversion, a critical point in the growth of uterus and welfare of fetus, are at present being applied to the human being by one of us (E. C. G.) and will be reported upon at a later date.

### Summary

1. The concept of uterine accommodation of the products of conception is briefly stated.
2. A method of analysis used in examining soft tissue x-rays of the gravid rhesus monkey uterus is given.
3. Results of these analyses suggest that on or shortly after the 100th day of gestation an important change in the pattern of uterine growth occurs. This consists of a relatively rapid elongation from a spherical to a cylindrical organ.

4. Supporting evidence consisting of changing vascular patterns and changing patterns of uterine weight gain and fetal growth is given.

5. This mechanism at once implies that the onset of labor is, in part at least, governed by the degree of uterine growth which occurs prior to conversion and that fetal maturity at birth is related to the length of the post-conversional phase. Further implications are possible.

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## PRIMARY ENDOMETRIOSIS OF THE VAGINAL PORTION OF THE CERVIX UTERI

R. S. SIDDALL, M.D., AND H. C. MACK, M.D., DETROIT, MICH.

*(From Harper Hospital and Wayne University College of Medicine)*

WITH one possible exception (Novak), references indicate that primary growth of ectopic endometrium on the uterine cervix is very rare. Most lesions of the cervix are obviously secondary to endometriosis of the recto-vaginal septum. Extension from the uterine corpus is also mentioned, though we have never seen such an instance. Likewise to be excluded is so-called adenomyosis of the cervix (cervical gland endometriosis, or cervicosis) as described by Teacher and further studied by von Torzay-Kiss, Salles, and others. This condition consists of more or less questionable invasion of cervical stroma by glands which are cervical in origin, or possibly from remnants of the mesonephros, and definitely not endometrial. Also not to be included are decidua-like changes of the cervical mucosa associated with pregnancy. There is little evidence here of glandular structure but rather surface changes which are largely stromal in appearance. In several cases examined after pregnancy, there was no suggestion of endometriosis.

We have been able to discover reports of only six cases of primary endometriosis of the cervix in a rather thorough review of the literature. Although Novak stated that he had "... seen a number of instances of endometriosis of the cervix uteri," it was not clear whether or not he was referring to primary involvement. In the last nine years we have found four certain or probable instances in our practices, and another probable one among the clinic patients at Harper Hospital. In addition to the question of the frequency of primary endometriosis of the cervix, the condition is of interest in regard to its etiology, and also because of its resemblance to carcinoma.

Essential points in the case reports found in the literature follow:

1. Fels, 1928: Nullipara, aged 33 years. History of uterine curettage in 1920, an attack of salpingitis in 1924, and abdominal suspension of the uterus in March, 1927. Six months later from a scar on the left side of the cervix were excised three red, lentil-sized nodules which proved to be typical endometriosis.

2. Rushmore, 1931: Patient's age, 26 years. Delivery in 1927 was followed by severe hemorrhage from a laceration beneath the urethra. Appendectomy and right salpingectomy in 1930. In 1931 a polypoid nodule from the right side of the external cervical os showed typical decidua lying beneath the stratified squamous epithelium. Later a uterine curettage yielded tissues of a normal pregnancy, and laparotomy showed essentially normal pelvic organs.

3. Fobe, 1940: Patient aged 23 years. Uterine curettage and round ligament suspension were soon followed by pregnancy, and then spontaneous abortion at three months. Eighteen months later while in the third month of the second pregnancy there was slight bleeding from an elevation the size of a hazelnut on the anterior cervical lip. This was excised and was diagnosed endometrioma with deciduel reaction. The pregnancy was undisturbed.

4. Henriques, 1941: Patient aged 40 years. Nine deliveries with the last one eight years before. A soft, bleeding mass the size of a hen's egg, which proved to be a hyperplastic endometrial growth, was removed from the vaginal portion of the cervix. The cervix was then amputated.

5. Hobbs and Lazar, 1941: White woman, 40 years old. There had been full-term deliveries twelve and fourteen years before, and nine years ago uterine suspension, bilateral salpingectomy, and left oophorectomy. Panhysterectomy was performed for menorrhagia. In addition to fibroids of the uterus, there was a small papillary body in the cervical canal near the external os which showed typical endometrial glands imbedded in stroma.

6. Lash and Rappaport, 1943: White woman, 31 years old. Full-term deliveries in 1926 and 1928, and two induced abortions. Slight vaginal bleeding at times for three years ceased after a small, dark red area was removed from the anterior lip of the cervix. This proved to be endometrial tissue partly covered by stratified squamous epithelium. The patient was well eighteen months later.

Lash and Rappaport proposed certain criteria favoring a diagnosis of primary endometriosis of the cervix. These have been altered and abbreviated as follows: (1) localization of the lesions on the anterior cervical lip or to one side of the external os; (2) an island of endometrial glands on the vaginal portion of the cervix, beneath the stratified squamous epithelium or exposed on the surface; (3) an endometrial island lying in scar tissue; (4) absence of evidence of extension from endometriosis involving the uterus, rectovaginal septum, or vaginal wall; (5) cessation of symptoms after eradication of the lesion.

The five cases we have to report are as follows:

CASE 1.—R. G., a white woman, was 35 years of age in 1939 when endometriosis of the cervix was discovered. She had had full-term deliveries in 1928 and 1931, and in 1937 uterine curettage was performed with removal of a uterine polyp. In 1939 curettage was done for incomplete abortion. Two slightly raised, round, purplish areas were seen on the anterior cervical lip to either side of the midline and in locations which could have represented the sites of tenaculum punctures at the first curettage. Both lesions were removed and gave the same microscopic picture of typical decidual reaction of stroma and glands covered over by the cervical squamous epithelium (Fig. 1). In February, 1948, panhysterectomy was done for increasing menorrhagia. In addition to multiple leiomyofibromas of the uterus, there was one small area of adenomyosis of the uterine wall. There was no suggestion that this isolated lesion could have had anything to do with the endometriosis of the cervix nine years before.

CASE 2.—A. A. was a white woman, 37 years old. She had a low forceps delivery in 1943 after a 3 cm. obliquely right and anterior incision of the elongated anterior lip of the cervix. Eight weeks later cervicitis was treated by cauterization. Examination in 1946 because of slight vaginal bleeding showed a small, bright red, slightly raised, round lesion just to the right of the external os and in the scar resulting from the incision of the cervix. The lesion was removed and the site thoroughly cauterized. Microscopic examination showed a nest of typical endometrial glands and stroma beneath the stratified squamous epithelium.



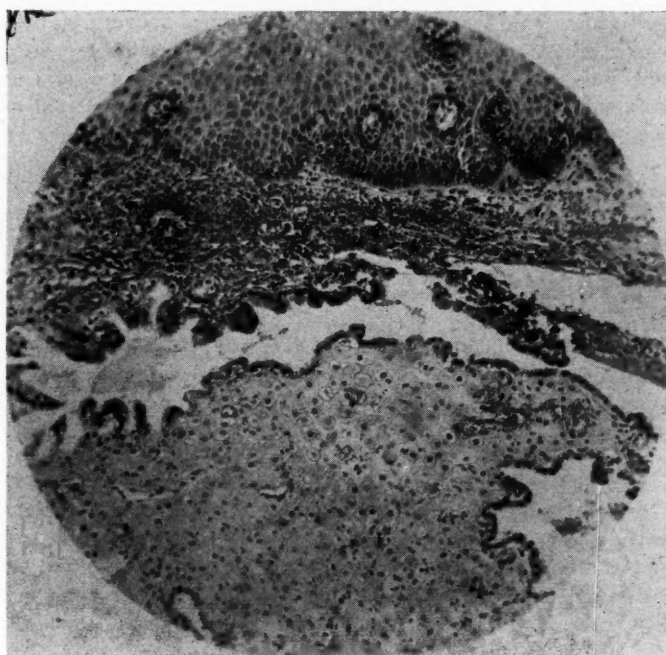


Fig. 1 (Case 1).—Pregnancy changes of glands and stroma in endometriosis of the cervix. Cervical squamous epithelium: above.

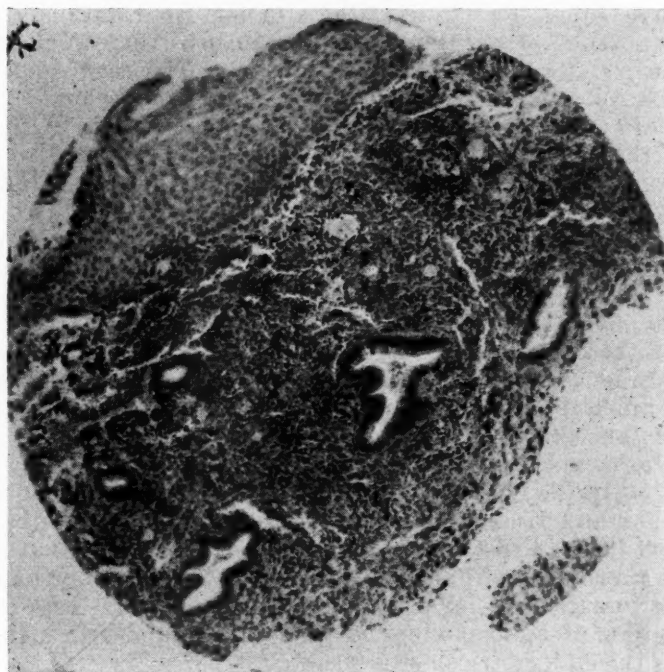


Fig. 2 (Case 3).—Glands and stroma of cervical endometriosis lying beneath the squamous epithelium covering.

CASE 3.—T. C. was a white woman, 25 years old. The first pregnancy in 1942 ended in spontaneous abortion at three months. She had a full-term delivery in 1943, with cauterization treatment of cervicitis afterward. Three years later an examination because of right lower abdominal quadrant pain showed the uterus retrodisplaced with tenderness on the right side but no palpable enlargement of the adnexa. Just outside the external os and opposite each other on the anterior and posterior cervical lips were two red lesions about 5 mm. in diameter. These were removed and microscopically proved to be nests of typical endometrium beneath the squamous epithelium (Fig. 2). The next year there was another uneventful delivery. Subsequent examinations showed the uterine and adnexal findings as before.

CASE 4.—B. G. was a white woman, 38 years old. After the birth of her seventh child in 1946 she complained of urinary stress incontinence on straining and coughing. There had also been frequent though slight vaginal bleeding. In addition to vaginal outlet relaxation, there was a small, red, raised area on the anterior cervical lip. This lesion was removed and was found to consist of endometrial glands and stroma which were covered, except for a small part, by stratified squamous epithelium. This patient reportedly died in 1948 of breast carcinoma with widespread metastases.

CASE 5.—R. R. was a white woman, 31 years old, with deliveries in 1941, 1944, and December, 1946. About two years later she was examined because of slight bleeding for three to four days preceding menstrual periods. There were about a half a dozen purplish, punctate areas on the anterior cervical lip, of which three were removed. Microscopically these showed endometrial glands and stroma situated beneath the stratified squamous epithelium of the cervix.

Among these eleven reported cases there are four in which, because of operative inspection of the pelvic organs in two (Fels, Rushmore) and in two with the additional examination of the completely removed uterus (Hobbs and Lazar, and our first case), extension of endometriosis from other organs to the cervix can be ruled out. In five others (Fobe, Henriques, and our Cases 2, 4, and 5) the absence of anything pointing to involvement elsewhere makes primary cervical endometriosis highly probable. The case reported by Lash and Rappaport and our third one are more doubtful because of pelvic findings which could possibly have been due to endometriosis of the adnexa. It is interesting that in three instances (Fobe, Rushmore, and our first case) the endometrial transplants in the cervix had undergone decidual changes in response to pregnancy.

The etiology of endometriosis of the cervix is largely a matter of conjecture. The Müllerian source of the cervical mucosa has suggested the possibility of mutation into endometrium, but Hobbs and Lazar found no facts in support of this idea. A more likely origin appears to be transplantation of endometrium to the cervix, as occurs sometimes in the vagina and perineum. Fuchs successfully grafted endometrium from the supravaginally removed uterus to the remaining cervix. In view of the many injuries to the cervix by labor, abortion, infection, and operation, with the frequent presence of endometrial fragments, endometriosis of the cervix might be expected commonly. Apparently the cervix is generally unsuitable for the growth of endometrium. Hobbs and Lazar suggested vaginal acidity as the inhibiting factor. In support of the transplantation idea, it is significant that in the eleven reported cases there was without exception a history of labor or operation as a cause of a traumatic site for transplantation. Our first case strongly suggests implantation of endometrium in tenaculum punctures. In our second case and Fels's the endometriosis was situated in old scars.

Endometriosis of the cervix has some gross resemblance to carcinoma and also may cause abnormal bleeding. A positive diagnosis is made from examination of a biopsy specimen, and the lesion should then be eradicated

by the actual cautery or excision. Finally, should experience confirm our observations regarding the relative frequency of primary endometriosis of the cervix, the question must arise as to its possible role in the etiology of adenocarcinoma of the cervix.

### Summary

Although only six authentic or probable instances of primary endometriosis of the cervix were found in the literature, the fact that we were able to add five more suggests that the growth is not uncommon. The condition probably has its origin in the transplantation of fragments of endometrium to traumatized areas on the cervix. Clinically, the endometrial areas have some resemblance to carcinoma. A diagnosis can be readily made by microscopic examination of a tissue biopsy. The lesion may then be destroyed with the cautery or excised. The part played by endometriosis in the origin of adenocarcinoma of the cervix uteri is as yet purely speculative.

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## PREGNANCY ASSOCIATED WITH HYPERTENSION AND INTRACRANIAL HEMORRHAGE\*

MILTON J. GOODFRIEND, M.D., F.A.C.S., MILTON D. KLEIN, M.D., F.A.C.S., AND JOSEPH M. SMOLEV, M.D., NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, Morrisania City Hospital)*

THE incidence of intracranial hemorrhage as a complication of pregnancy is infrequent and is generally thought to be a result of hypertension. A recent experience with this complication has led one of us (M. D. K.) to review the cases of all patients with cerebrovascular hemorrhage which occurred on the Obstetrical Service of the Morrisania City Hospital. Five such cases were found among 25,000 deliveries from 1930 to 1948, an incidence of one in 5,000 pregnancies. These cases are summarized as follows:

CASE 1.—Mrs. M. S., a 31-year-old gravida ii, para i, registered in the prenatal clinic on Aug. 11, 1947. Her last menstrual period occurred Jan. 20, 1947, and the estimated date of confinement was Oct. 27, 1947. Her history revealed the following: In 1945 she had a normal spontaneous delivery following which her blood pressure was 150/100 and remained elevated during the immediate postpartum period. At that time the Kahn test was positive (four plus). In January, 1946, she was admitted on the surgical service for a local swelling beneath the left jaw and the blood pressure was 150/100.

The prenatal examination revealed no physical abnormalities. She weighed 149½ pounds, the blood pressure was 142/90; the urine and Wassermann were negative. During her pregnancy she was given a salt-free diet for her hypertension. Her prenatal course was uneventful until Oct. 24, 1947, when she gained 8½ pounds between her regular fortnightly visits. The blood pressure was found to be 148/98 and the urine negative. Hospitalization was advised.

That day the membranes ruptured spontaneously and she returned to the hospital. On admission she was in labor; vertex presenting as right occipitotransverse; head engaged, cervix dilated 2½ fingers. A catheterized specimen of urine contained one plus albumin and occasional white blood cells; the specific gravity was 1.014. Her blood pressure was 168/110. She developed strong and frequent contractions and the following morning delivered spontaneously a living child. The blood pressure during labor was 185/108. Ten hours post partum she complained of severe pain in the back of her neck and around the shoulders. She vomited large quantities of undigested food and became very drowsy. The blood pressure was 220/130. A pre-eclamptic routine was instituted. For several days there was very little change in the clinical course. The blood pressure varied between 188/130 and 150/108. The urine showed two to three plus albuminuria. On Oct. 29, 1947, neck rigidity was noted, and the temperature had risen to 101° F. She was given penicillin. A neurological consultation was requested; the findings were marked nuchal rigidity, opisthotonus, and depressed but equal tendon reflexes, negative Kernigs, and no Babinski. The fundi showed slight blurring of both discs. The diagnosis was subarachnoid hemorrhage. Meningitis, bacterial or toxic, was considered as a second possibility. Lumbar puncture was performed and revealed an initial pressure of 320 mm. water; the final pressure was 115 mm. of water with an Ayala index of 3.6 per cent. Microscopic examination showed 1,870 white cells, of which 86 per cent were polymorphonuclear leucocytes; the red cells 125,000; the Wassermann, Kahn, and cultures were negative. Following the lumbar tap the headache was relieved for several hours. The blood pressure was 170/108. Intravenous glucose and magnesium sulfate were administered. Subsequent spinal taps showed a progressive decrease in pressure with gradual

\*Presented before the Bronx Gynecological and Obstetrical Society, May 24, 1948.



disappearance of gross blood. The patient continued to improve and on the tenth day post partum showed only a slight stiffness of the neck. The blood pressure was 128/80. Ophthalmoscopic examination showed a moderately narrowed arterial tree with some increase in the light reflex indicative of pre-existing hypertension. She left the hospital against advice on the sixteenth postpartum day at which time her blood pressure was 136/84 and the urine continued to show a two plus albumin reaction.

Four and one-half months after delivery, she returned to the follow-up clinic. The pressure was 128/80; the urinalysis and blood chemistry were normal. The visual fields were within normal limits. The Kahn and Mazzini tests were reported as two plus. Neurological findings were considered normal.

*Summary and Comment.*—This multipara, a known hypertensive, developed signs of toxemia in the latter part of the second pregnancy manifested by elevation of blood pressure above the prepregnancy level, albuminuria, edema, and retinal changes indicative of hypertensive vascular disease.

The intracranial lesion which aggravated the symptoms was subarachnoid hemorrhage, proved by spinal tap. The symptoms of headache, vomiting, drowsiness, increased albuminuria, and elevated blood pressure were mistaken for impending eclampsia. Neurological examination revealed the true nature of the condition and proper therapy then hastened her recovery.

Despite the presence of an equivocal positive serology, syphilis was not considered the causative factor. It is known that syphilis is rarely the cause of subarachnoid hemorrhage, and intracranial aneurysms are practically never due to this disease. In fact, most of the cases of subarachnoid hemorrhage in syphilitics are due to a coincidental aneurysm or rupture of a vascular anomaly.

This case therefore illustrates the presence of a true toxemia (pre-eclampsia) engrafted upon a pregnancy hypertension, further complicated by subarachnoid hemorrhage, with resulting recovery.

CASE 2.—Mrs. L. M. J., a 23-year-old Negro gravida ii, para i, visited the prenatal clinic on April 4, 1945. Her last menstrual period was on Sept. 15, 1944. Her expected date of confinement was June 22, 1945. As a child she had malaria and typhoid fever but no kidney disease. Her previous pregnancy was associated with hypertension. A communication from Fordham Hospital where she was delivered in 1944 stated that she had had hypertension and had been treated for toxemia. Her sister who accompanied her explained that for the past one and one-half years she had had headaches, dizzy spells, and spots before the eyes and that she was under treatment by her family doctor for high blood pressure. Examination revealed a blood pressure of 130/84, a normal urine, and negative serology. General physical examination revealed no abnormalities. During her prenatal course there was a gradual rise in blood pressure until at the thirty-fifth week of her pregnancy the blood pressure was 150/100 and a faint trace of albumin was present in the urine. Hospitalization was advised.

She failed to enter the hospital until two weeks later. On admission she complained of occipital headaches, dizziness, spots before the eyes, and weakness. Examination revealed a full-term pregnancy with the vertex engaged. There was moderate ankle and hand edema. The blood pressure was 185/130. The eyegrounds showed a moderate degree of tortuosity of the retinal vessels. Laboratory findings were as follows: The urine had a specific gravity of 1.012, two plus albumin with occasional red and white cells. The blood chemistry showed a urea nitrogen of 9.5 mg. per cent and a uric acid of 3.3 mg. per cent. Magnesium sulfate was given intravenously for dehydration. The following morning labor started and she had strong uterine contractions. The blood pressure increased to 220/150. In the early part of the evening, June 4, 1945, she delivered spontaneously a living male child. Shortly afterward, she complained of severe headache, became very restless and uncooperative. Sedation was given. In the morning it was noted that she was semistuporous. Neurological consultation revealed a right hemiparesis, unequal pupils with the right larger than the left. There was forced conjugate deviation of the eyes to the right; meningeal signs were absent. A diagnosis of subarachnoid hemorrhage was made. Lumbar puncture revealed an initial pressure of 270 mm. water and contained chlorides 704 mg. per cent, sugar 59 mg. per cent and

the total proteins 36 mg. per cent. The smears were negative and the cultures showed no growth. No gross blood was noted. A catheterized specimen of urine contained one plus albumin with occasional white blood cells and 10 to 20 red cells. The temperature reached 102° F. A second spinal tap the next day revealed a cloudy fluid; the initial pressure was 252 mm. water with an Ayala index of 8.4 per cent. Spinal fluid chemistry showed sugar 3.1 mg. per cent, chlorides 789 mg. per cent, and protein 33.2 mg. per cent. Microscopic examination revealed many red blood cells, mostly crenated, indicating that the blood in the spinal fluid was not traumatic but due to bleeding into or from the meningeal spaces. At this time nuchal rigidity was noticed and the blood pressure was 190/130. Despite therapy the patient became progressively worse, developed a pulmonary edema, and expired on June 8, 1945, four days post partum.

*Summary and Comment.*—This multigravida with a hypertension during her first pregnancy that persisted between pregnancies, developed a pre-eclamptic toxemia between the thirty-first and thirty-third week of her current pregnancy, manifested by the appearance of a marked rise in blood pressure, albuminuria, and edema. During labor there was a further increase of 35 mm. Hg during the systolic phase and 20 mm. Hg during the diastolic phase.

Although her symptoms immediately post partum were indicative of intracranial complication, it was not suspected until she became stuporous and developed a hemiparesis fifteen hours after delivery.

This case illustrates, as does the preceding one, the presence of a superimposed toxemia in a patient with pregnancy vascular hypertension which terminated fatally from subarachnoid hemorrhage.

CASE 3.—Mrs. J. M., a 32-year-old white woman, gravida vi, para v, entered the hospital on July 19, 1939. Her chief complaints were headache, vertigo, spots before the eyes, and ankle edema of two months' duration. Her last menstrual period was Dec. 18, 1938. The expected date of confinement was Sept. 25, 1939. Previous history revealed that she had been delivered nine years ago in Malta at which time she had kidney disease with high blood pressure and hematuria.

On admission the blood pressure was 155/98 and there was moderate ankle edema. A catheterized specimen of urine contained a one plus albumin reaction with numerous hyaline and granular casts. The Fishberg concentration test showed a fixation of the specific gravity at 1.010. The blood chemistry revealed urea nitrogen 13.5 mg. per cent and the sugar 89 mg. per cent. With bed rest, restricted fluids, and salt-free diet, the headaches improved and the edema gradually diminished. On July 31, 1939, the headaches recurred and the blood pressure was 160/100. A twenty-four-hour urine specimen contained 3.4 Gm. albumin. A second blood chemistry revealed a uric acid of 8.8 mg. per cent, urea nitrogen 40 mg. per cent, and the serum protein 8.5 mg. per cent. In view of the evidence of increasing renal damage, it was decided to terminate the pregnancy. A medical induction of labor was tried but was unsuccessful. Catheters were then introduced into the uterus. After one-half hour of labor she complained of severe headache, had a convulsion, and became comatose. The blood pressure reading was 200/130. The spinal fluid was under increased pressure and grossly bloody. She died shortly thereafter, undelivered, without regaining consciousness. The diagnosis was subarachnoid hemorrhage.

*Summary and Comment.*—Previous history indicated that she had a nephritis associated with hematuria and hypertension during her first pregnancy. Aggravation of this kidney condition during her current pregnancy was manifested by a rise in blood pressure, particularly the diastolic; an increase in albuminuria and evidence of azotemia. This case terminated fatally not by uremia as would be expected but by intracranial hemorrhage.

CASE 4.—Mrs. M. T., a 40-year-old white woman, gravida v, para iv, was admitted to the Medical Service on Feb. 13, 1936, in a semiconscious state, restless with sterterous respirations and a paralysis involving the right side of the body. The following history was obtained from the husband. She was a known hypertensive and had a "stroke" eleven years ago. She was seven and one-half months pregnant and had had no prenatal care. Two weeks prior to admission she complained of headaches. Two hours before admission the headache became severe, she fell forward and lost consciousness.

On admission the blood pressure was 170/110. There was no evidence of external injuries. She was seven and one-half months pregnant but no fetal heart tone was audible. There was evidence of right organic hemiplegia with a positive right Babinski; the reflexes on the right were increased and the abdominals on the same side were absent. There was two plus ankle edema. The heart showed definite enlargement. Examination of the eyes showed a drooping of the right lid; the pupils reacted to light; the optic discs were edematous, the edema extending to the surrounding retinal tissues. Hemorrhages and exudates were seen particularly in the neighborhood of the discs. The arteries were contracted; the veins dilated. Symmetrical colobomas were noted extending through the ciliary body and choroid but not through the optic nerve. Ophthalmoscopic diagnosis was hypertensive retinopathy with congenital colobomas of the uveal tract.

The pertinent laboratory findings were as follows: The Wassermann and Kahn were negative; the blood chemistry was within normal limits. The urine was reddish brown color, acid reaction with four plus albumin and containing numerous granular casts; there were 40 to 50 white cells. The spinal fluid was clear; the initial pressure was 208 mm. water; the final pressure was 95 mm. water. The protein was not increased; the sugar was faintly positive and microscopic examination showed 130 red blood cells. The smears and culture were negative. The clinical impression was (1) malignant phase of essential hypertension and (2) cerebral accident.

She remained on the medical service where therapy consisted of hypertonic glucose solution intravenously and sedation. The following day she continued to be restless, irrational, and comatose. The blood pressure was 170/120. The onset of labor was not noted because of her restlessness and stupor until she delivered a premature stillbirth in bed. The blood pressure had risen to 220/130. At this time she bled profusely per vaginam and was immediately transferred to the obstetrical service where a manual removal of the placenta was done and the uterus packed. Despite therapy she failed to improve, became cyanotic, and one hour after delivery expired.

*Summary and Comment.*—This case illustrates the effect of pregnancy in a patient with long-standing hypertensive cardiovascular disease. The history of a previous stroke was evidence of an existing severe intracranial vascular pathology which made the vessel wall increasingly susceptible to rhesis. The hypertension became clinically malignant resulting in a cerebral accident.

**CASE 5.**—Mrs. E. C., a 37-year-old white woman, gravida ii, para i, whose last menstrual period occurred on July 1, 1935, visited the prenatal clinic for the first time on Dec. 23, 1935. Her expected date of confinement was April 8, 1936. There was no history of renal disease. The blood pressure was 140/90. A voided specimen contained an occasional white blood cell. The blood count was 4.2 million red cells and the hemoglobin 80 per cent. The serology was negative. The blood chemistry and electrocardiogram were normal. Six weeks later because of headaches, ankle edema, and elevated blood pressure, she was referred to in the hospital from the prenatal clinic. On admission the blood pressure was 148/94. After several days she was discharged with a blood pressure of 140/80. It was believed that she had an essential hypertension.

On Feb. 25, 1936, she was readmitted because of vaginal bleeding of four days' duration. Moderate ankle edema was observed and the blood pressure was 170/110. Analysis of the urine revealed a trace of albumin, few hyaline casts with occasional white cells. Because of the vaginal bleeding she was typed, cross matched, and then examined vaginally (with the operating room set up for possible cesarean section). The cervix was two fingers dilated, the vertex presenting, and the margin of the placenta was palpated anteriorly and along the right edge of the cervix. A diagnosis of placenta previa was made. A No. 6 Voorhees bag was inserted extraovularly and a one-pound weight attached. After five hours of strong uterine contractions, the patient was fully dilated and expelled the bag. The blood pressure was 190/120. The membranes were then ruptured artificially and a living child was delivered by version and extraction.

One hour and forty minutes later the patient complained of severe pain in the head. The following day she was drowsy; the temperature was 102° F. and the blood pressure



reached 190/130. The reflexes were hyperactive; there was definite neck rigidity and evidence of right hemiparesis. The pupils were dilated (under mydriasis) and showed congestion; the discs were normal but small hemorrhages were seen in the right retina. The spinal fluid obtained by lumbar puncture was bloody and under increased pressure. The initial pressure was 15 mm. water and the final tap was 6 mm. water. The red cells were crenated, indicating a nontraumatic tap. The diagnosis was subarachnoid hemorrhage secondary to hypertensive vascular disease. The urine contained four plus albumin, many granular casts, few red cells and an occasional white cell. The urea nitrogen was 25 mg. per cent. Despite therapy the patient failed to improve; she developed pulmonary edema and expired on Feb. 29, 1936.

*Summary and Comment.*—This patient had a blood pressure of 140/90 before the twenty-fourth week of her pregnancy. A sustained pressure of 130 to 140 mm. Hg systolic and 85 to 90 mm. Hg diastolic during the early months of pregnancy is frequently indicative of pre-existing hypertensive disease.<sup>1</sup> The increase in blood pressure to 170/110 during the latter part of her pregnancy must be evaluated with the knowledge that nearly 40 per cent of patients with hypertensive disease show a rise of more than 20 mm. Hg over the blood pressure level of midpregnancy.<sup>2</sup> This fact makes the diagnosis of superimposed toxemia in a patient with hypertension often very difficult. However, in this patient the laboratory findings were more in accord with essential hypertension than with toxemia. Although cerebral hemorrhage may occur at any period in the course of essential hypertension, it is more frequent in those cases in which there are fluctuations in blood pressure.<sup>3</sup>

This case is considered one of essential hypertension aggravated by pregnancy which terminated fatally because of subarachnoid hemorrhage.

### Discussion

Of the five cases presented in this study, four died. Cerebrovascular accidents of such severity require careful analysis. In searching for factors which might play an important role in the sequence of events leading to intracranial hemorrhage, the following deserve special comment: (1) hypertension, (2) toxemia, (3) pregnancy and labor.

*The Role of Hypertension.*—Normal arteries can withstand very high pressures over very long periods of time without rupture.<sup>4</sup> When rhexis of a blood vessel does occur there must be underlying disease or a congenital anomaly of the vessel wall. In recent investigations on cadavers, it was found that even with pressure as high as 1,520 mm. Hg, Lampert and Mueller<sup>5</sup> were able to rupture the cerebral vessels in only two of the thirty cadavers, and both of these were in syphilitic individuals.

It is safe to presume that the patients in the cases presented above had some pre-existing lesion in the vascular system. All of the patients had a pre-existing hypertension. Three had essential hypertension, one had chronic nephritis, and the other, cardiovascular disease. Where fundoscopic examinations were made there was evidence of vascular changes reflecting similar pathology of the cerebrovascular system. These lesions, as stated above, predisposed such patients to a possible cerebral accident when the blood pressure increased beyond the level to which the vessel walls had been accustomed.

High blood pressure therefore may become a precipitating or contributing factor in intracranial hemorrhage if there exists some underlying pathology of the cerebral vessels.

*The Role of Toxemia.*—Toxemia of pregnancy either occurs in women who are otherwise normal or may be superimposed on patients with existing hypertension. Toxemia (nonconvulsive type) seldom causes cerebral accidents in those who are otherwise normal. This is not surprising in view of the fact that such toxemias are more common in women during their first pregnancies. Most primiparas are young, usually in their early twenties, with a normal vascular tree and free from previous hypertension. The hypertension



in this type toxemia usually averages 140 to 170 systolic and 90 to 110 diastolic unless the condition is very severe. The hypertension is usually of short duration because patients with adequate care will be properly treated, and where treatment fails, the pregnancy is terminated. However, where toxemia complicates a pregnancy hypertension, the vessel spasm and its associated rise in blood pressure will add further strain to the vessel walls, predisposing them to rupture. This was the possible sequence of events in Cases 1 and 2. The existence of toxemia in such pregnancy undoubtedly speeds up the normal progressive changes of hypertension.

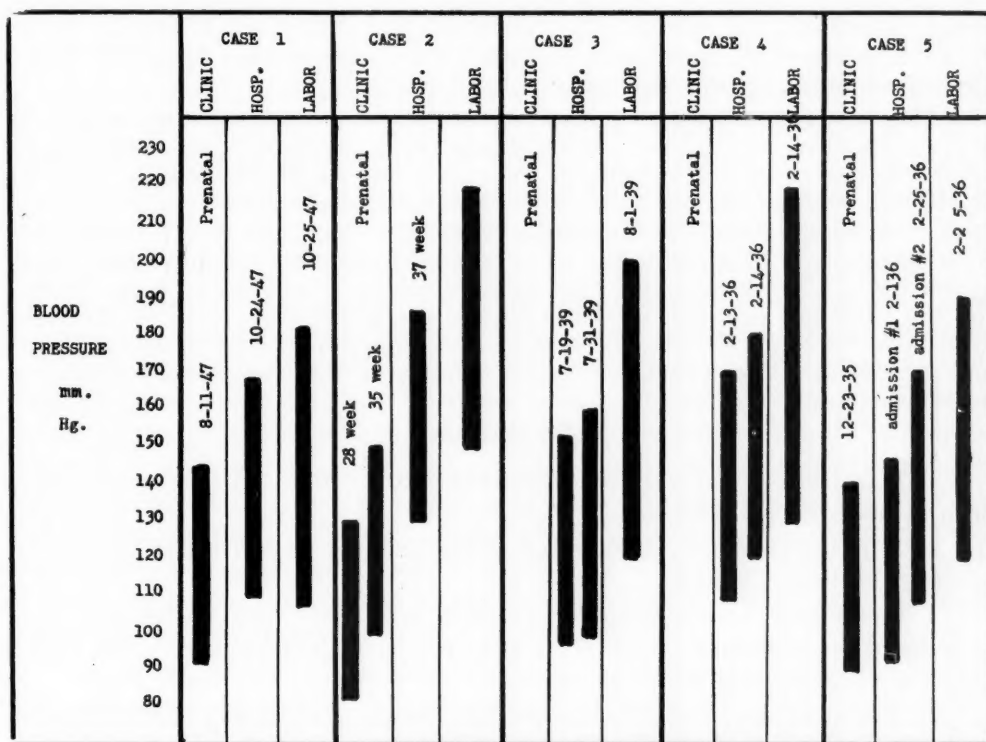


FIG 1. VARIATIONS IN BLOOD PRESSURE IN PREGNANCY AND LABOR

Cerebrovascular hemorrhage in pregnant women with hypertension often passes unrecognized. This is particularly true in patients with pre-existing hypertension and coexisting toxemia, since their combined effects are cumulative particularly with reference to the central nervous system. The headaches, drowsiness, hypertension, and increasing albuminuria are attributed to an aggravation of the toxemia or of the pre-existing hypertension rather than to the vascular accident, thus causing the true nature of the lesion to be overlooked. This was illustrated in Cases 1 and 2. It should be emphasized that adequate neurological examination must be performed and repeated if necessary in all pregnant women with hypertension who show aggravation of their cerebral symptoms, and especially in those with superimposed toxemia, if one is to recognize this complication and institute proper therapy. Lumbar puncture may often be necessary to determine the true situation.

*The Role of Pregnancy and Labor.*—All the patients were seven and one-half months pregnant or more at the time of the cerebrovascular accident. It is known that during this phase of pregnancy the increased blood volume and circulating load exert their greatest strain on the cardiovascular system.

Fluctuations in blood pressures occur during labor and especially during the second stage.<sup>4, 5</sup> In our small series the highest rise was obtained during labor; the systolic reached approximately 200 mm. Hg or more and the diastolic 120 mm. Hg or more. Although cerebral hemorrhage may occur at any period in the course of hypertension, it is more frequent where fluctuations in blood pressure exist. The variations in blood pressure before and during labor are shown in Fig. 1. Since it is apparent that fluctuations in blood pressure associated with labor may be a precipitating factor in vascular accidents, any measure which will avoid rises in pressure may prevent the development of this serious complication. These measures are: (1) the alleviation of painful stimuli by adequate sedation; (2) the relief of labor pains by proper anesthesia, i.e., caudal; (3) the elimination of the second stage of labor. In all hypertensives, regardless of cause, there should be a complete avoidance of all undue stress and strain.

The active treatment of cerebrovascular hemorrhage in pregnancy is lumbar puncture; additional measures are merely symptomatic. Prophylaxis offers the best hope for salvage of lives from this accident. Where evidence of chronic nephritis exists or where vascular pathology is evident, as in those with a previous intracranial accident, pregnancy should be avoided. Patients with essential hypertension may be permitted to become pregnant only in selected cases. The pregnancy must be carefully observed with proper regard for the increased incidence of toxemia and terminated as soon as untoward symptoms develop. On the other hand, if a patient with known hypertension had developed toxemia in a previous pregnancy, future pregnancies should be prohibited.

### Conclusions

1. Five cases of intracranial hemorrhage associated with pregnancy have been presented and discussed.
2. It is believed that a vascular lesion existing before pregnancy is the basis for such hemorrhage.
3. Labor and/or superimposed toxemia may be the precipitating factors because of the increased blood volume, the increased blood pressure, the fluctuations in pressure, and increased strain.
4. Adequate neurological examination or consultation in pregnant women with hypertension, albuminuria, and edema is advisable, especially in those with cerebral symptoms.
5. In those women with a past history of hemorrhage from rupture of an intracranial blood vessel, future pregnancies should be avoided. If intracranial hemorrhage complicates an early pregnancy, therapeutic abortion is advocated as soon as the patient's condition permits. If such patients are not seen until late in pregnancy then cesarean section is the procedure of choice.

We wish to thank Dr. A. B. Tamis and Dr. N. Savitsky for their valuable suggestions.

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1882 GRAND CONCOURSE, BRONX.

## OBSERVATIONS ON THE DECIDUAL REACTION OF THE CERVIX DURING PREGNANCY

R. G. BAUSCH, M.D.,\* D. H. KAUMP, M.D., AND R. W. ALLES, M.D.,  
DETROIT, MICH.

(From the Departments of Obstetrics and Gynecology and of Pathology, Providence Hospital)

IN THE cervix during pregnancy two distinct changes occur. One involves the epithelium, which exhibits very marked proliferative activity,<sup>1, 4</sup> and the other is a reaction which involves isolated patches of mesenchymal cells to produce a decidual type pattern.<sup>6, 7, 10, 11, 13</sup>

The epithelial proliferative activity includes a marked increase in the size and tortuosity of the glandular elements and epithelial proliferation both of the cuboidal cells of the glands and the superficial squamous epithelium covering the cervix. The glands tend to be dilated and are filled with mucus. The proliferation may be so extreme as to form polyps or masses which appear occasionally as condylomatous tumors. The cervical epithelial hyperplasias of pregnancy have been divided into three types.<sup>1</sup> Type One is characterized by simple hyperplasia of the squamous epithelium, formation of large rete cones, presence of long narrow papillae, and increased frequency of epithelial mitosis; Type Two by epithelial cells which appear to be arranged around the papillary stalks, and prominent epithelial masses which are two or three times as thick as in Type One; and Type Three by papillary growths or condylomatous masses composed microscopically of large simple stalks with a multitude of papillary side branches covered with thick squamous epithelium.

The second change is less well known. This change, involving the stroma, is composed of an alteration of the mesenchymal cells to a decidual type cell. This type of change may occur early in pregnancy<sup>7</sup> although apparently it is more frequent at term and subsides with no notable complications following termination of pregnancy.<sup>3, 5</sup>

It becomes clinically important to distinguish the decidual reaction of the cervix during pregnancy from carcinoma, which it grossly resembles, because of the obvious difference in the prognosis in these two lesions and, further, the presence of decidual reactions may explain the tendency to bleeding in the early months of pregnancy and occasionally at term. Pathologically, it is important properly to diagnose this reaction because of its relation to pregnancy and to enable us to define truly the source of bleeding if such should occur. Willer mentioned that if the decidual reaction is in the lower two-thirds of the cervix it is considered to be ectopic decidual. Other authors, however, feel that the decidual reaction is a part of the general change of pregnancy and is not to be considered as an ectopic type of reaction.<sup>10</sup>

\*Present address: 1105 Merchants Bank Bldg., Cedar Rapids, Iowa.

Various theories as to the pathogenesis of cervical decidual islands have been proposed. Schock indicates that decidual islands may be brought down to the cervix during curettage. This theory is difficult to accept when one finds no history of either trauma or curettage in an individual patient. Frankl has indicated that an inflammatory stimulus is the principal predisposing factor. Meyer has modified this theory to indicate that decidual nests are found in the presence of local inflammatory irritation in a normal physiologic tissue which must have a certain innate pre-existing structure before decidual cells can be formed there. This opinion is strengthened when one finds that the decidual reaction in cervical polyps is very much more extensive and better developed than in the cervix proper.<sup>7</sup>

Grossly the lesions produced by decidual reaction of the cervix vary somewhat in character, although in general the appearance is very similar. This reaction in our cases was manifest as multiple, small, yellowish or reddish elevations varying from 0.5 to 2.0 cm. in diameter on the cervical mucosa. They were extremely soft, quite friable, and bled easily with slight trauma. These may be present as discrete nodules which vary in number or in form or as a raised plaque which covers portions of both the anterior and posterior lip of the cervix. The most severe lesion in our series was one in which the entire anterior lip of the cervix was composed of a very large fungating mass of tissue which displaced much of the cervix.

Microscopically the superficial epithelium is extremely thin and may even be partially eroded. The lesions are extremely vascular and are characterized in the typical late stages by decidual cells which are large, prominent, rounded cells often polygonal in shape. The cytoplasm is generally basophilic in color, is abundant, is occasionally vacuolated and is finely granular. The nuclei are relatively small, rounded, vesicular and some possess small nucleoli. In occasional areas the decidual cells are separated by edema (Figs. 2, 3, 4). Focal inflammatory reactions characterized by collections of lymphocytes and occasionally polymorphonuclear leucocytes are pronounced in some instances while in others the tissue surrounding the nests of decidual cells is quite normal in appearance except for a moderate edema and vascular dilatation. Except for the increased numbers and dilatation, the vascular channels are normal in appearance as are the lymphatic channels.

As we trace the typical decidual reaction backward to its beginning it is noted that the cells progressively become smaller in size, and eventually one finds that the cells are those of the mesenchyme composing the stroma of the cervix. The initial lesion, then, is one in which there is an edema with separation of the stroma fibers and swelling of the individual cells (Fig. 1). This reaction is noted first beneath the squamous epithelium or in the stroma immediately surrounding the glandular elements. The cervical glandular elements which are enclosed in the sheets of decidual cells are often distorted and are lined by flattened cuboidal epithelium. This marked distortion of the cervical glands may produce a picture suggesting endometrial glands. However, on careful search a transition to cervical glands can be found. The absence of



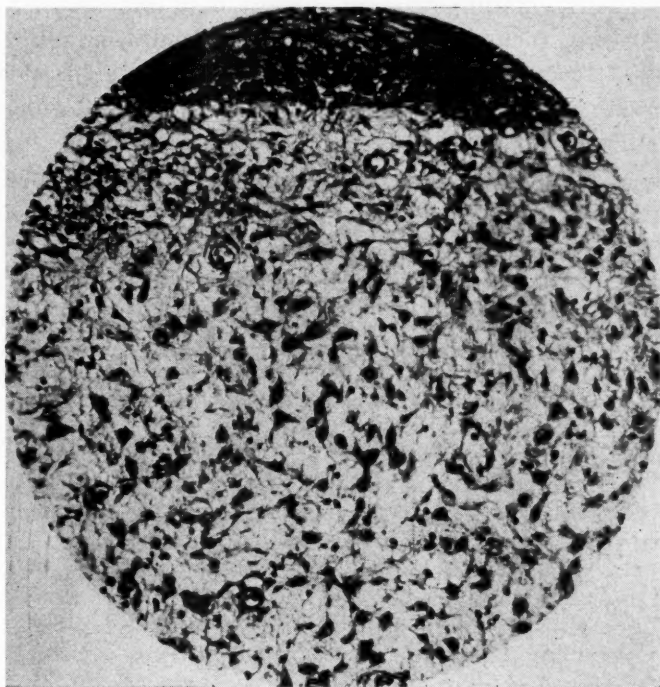


Fig. 1 (Case 2).—Intercellular edema with separation of stroma cells, swelling of cytoplasm, and tendency of the cells to become more round. ( $\times 275$ .)

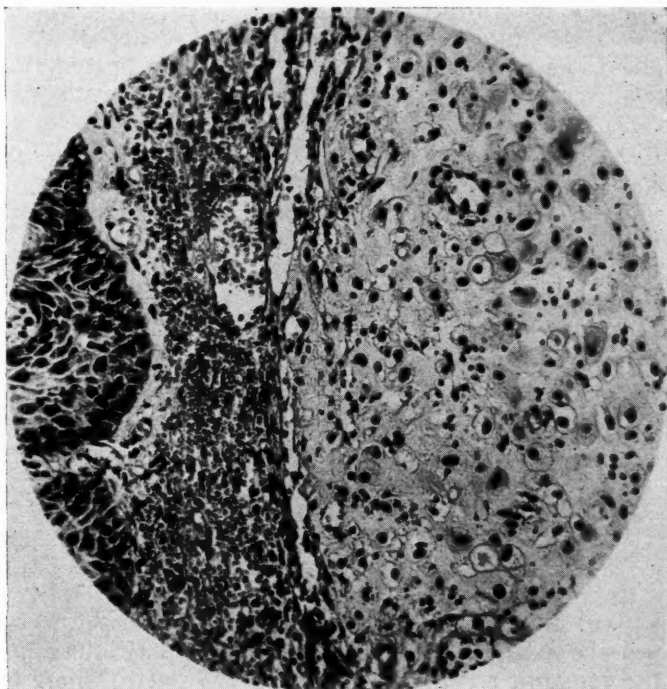


Fig. 2 (Case 6).—Further swelling of stroma cells accompanied by superficial squamous hyperplasia and increased vascularity. ( $\times 275$ .)

any marked evidences of inflammation suggest that inflammation is not necessarily a predisposing factor in the production of the decidual reaction in the cervix. Decidual reactions may also be seen in chronically infected tissue as was true in those of our three cases of decidual reaction which occurred in endocervical polyps.

The absence of endometrial glandular elements in our tissues indicate that ectopic endometrium is not necessarily present, although one would anticipate a decidual change in the uncommon case of cervical endometriosis. These changes appear to be more intense as pregnancy progresses. This indicates that the same pregnancy hormone effect which is operative in endometrial decidual change probably exerts a similar effect on the mesenchymal cells in the stroma.

### Material

Our material for this study consisted of two sources of specimens. The first included ten pregnant or postpartum uteri from which sections of the cervix were available. Of these, seven were obtained at necropsy and three from uteri removed surgically for other lesions. In this group there were eight pregnant and two postpartum uteri. The postpartum uteri were three weeks and three months, respectively, post partum. There was no decidual reaction in either. Of the eight pregnant uteri four had and four did not have any evidences of a decidual reaction. Of the four with no decidual reaction only one was a term delivery. The other deliveries were at 12, 26, and 32 weeks, respectively. Of the four patients with cervical decidual reaction two were at term and the other two were at one and three months' gestation, respectively. The ages of the women were 23, 25, 36, and 38 years. From this small group no conclusions can be drawn but trends can be noted. It seems significant that 50 per cent had a decidual reaction, none had evidence of endometriosis, or severe infection of the cervix, and that neither of the postpartum uteri had a decidual reaction suggesting that this reaction resolves with no demonstrable sequelae.

Our second source of material consisted of sixteen cervical biopsies in which a decidual reaction was present. Eight of these specimens were collected from our own material over a relatively short period of time and eight were loaned to us by Dr. D. C. Beaver, Pathologist, Women's Hospital, Detroit.

In this series of sixteen cases the period of gestation at the time of biopsy was known in eleven. These were distributed as follows:

TABLE I. PERIOD OF GESTATION AT WHICH BIOPSY WAS TAKEN

PERIOD	NUMBER
2 months	4
3 months	1
4 months	2
5 months	2
Term	2
Total	11

It is significant that four were diagnosed at two months' gestation. Of these four there was a history of vaginal bleeding in two and no available information in the remaining two. In regard to the parity, there is no apparent significance. The age was known in twelve cases and the average was slightly

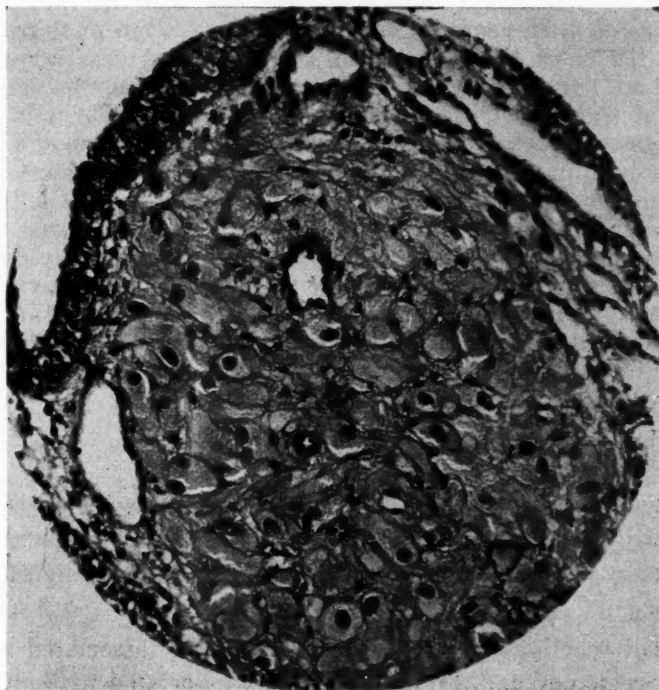


Fig. 3 (Case 4).—Small, well-localized clump of decidual cells. ( $\times 275$ .)

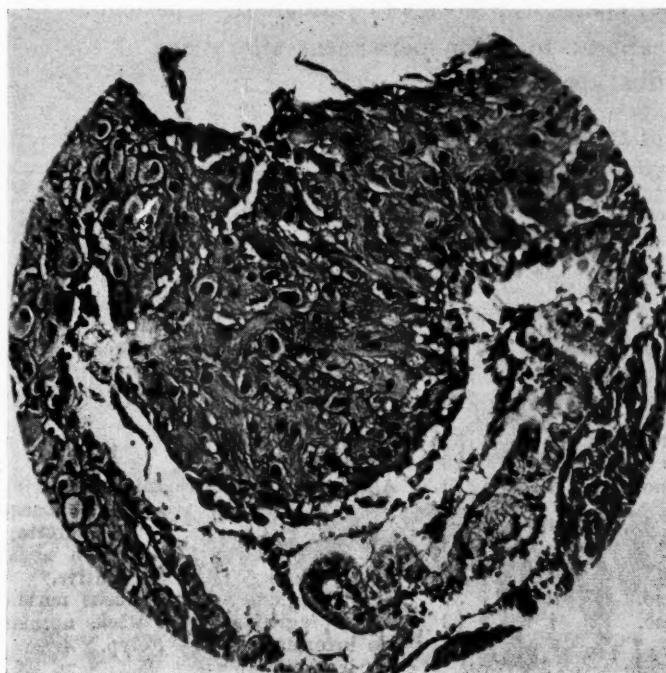


Fig. 4 (Case 15).—Masses of decidual cells arranged in subepithelial and periglandular areas. The gland epithelium is flattened and often distorted or partially lost. ( $\times 275$ .)

over thirty years which is a higher average age than we find in our routine delivery series (22 to 25 years in 1,441 deliveries of a recent four-month series). In eleven of the cases the outcome of the pregnancy was known. Of these, three aborted at variable periods from two to three months' gestation, while the other eight were term pregnancies. In this connection it is interesting to note that the cases reported by Klein and Domeier, Hennessy, and by Waldstein, all were term or approximately term pregnancies. This suggests that bleeding in early pregnancy caused by cervical decidual reaction is not invariably accompanied by abortion. In five of the sixteen cases there was definite knowledge as to the presence of vaginal bleeding, and vaginal bleeding was noted early in pregnancy in two of these, while the third had excessive vaginal bleeding at the time of birth of the child. In six cases the postpartum examinations which were done indicated that there was a complete resolution of the lesion following the termination of pregnancy. This is further borne out by our experience with the control material cited above.

### Summary and Conclusions

1. Decidual reactions of the cervix in pregnant women occur frequently and occasionally may account for bleeding during the early part of pregnancy and further may progress to such a degree as to produce significant bleeding at or near term.
2. Decidual reactions of the cervix are probably associated with the usual hormones of pregnancy and are not necessarily associated with either inflammation or endometriosis.
3. An awareness of this reaction on the part of the obstetrician and the pathologist may enable us properly to evaluate these patients.
4. There appear to be no permanent alterations of the cervix associated with this decidual reaction.

TABLE II. SUMMARY OF CASES WITH CERVICAL DECIDUAL REACTIONS

CASE	BIOPSY AT	PARITY	AGE	DELIVERY	COMMENTS
1	3 mo.	i	31	Term pregnancy	Irregular vaginal bleeding 6 weeks normal.
2	4 mo.	i	33	Term pregnancy	6 weeks normal.
3	5 mo.	ii	33	Term pregnancy	Follow up normal, no symptoms.
4		i	17	Term pregnancy	
5	2 mo.	i	23	Incomplete abortion	Profuse vaginal bleeding, one month.
6	2 mo.	iii	36	Incomplete abortion, 2 months	
7	Term	ii	31	Term pregnancy	
8	Term	v	28	Term pregnancy	
9	2 mo.	ii	29	Aborted at 3 months	Intermittent spotting 5 days; had subsequent dilatation and curettage; prior examination negative; follow up negative.
10	5 mo.	ii	36	Term pregnancy	6 weeks normal, no symptoms.
11	2 mo.	i	33	Term pregnancy	6 weeks normal.
12				No information	Polyp.
13				No information	
14				No information	
15	4 mo.	iii	32	No information	Polyp.
16				No information	



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## PYOMETRA: A CLINICAL AND PATHOLOGIC STUDY\*

ROBERT W. DeVoe, M.D., AND LAWRENCE M. RANDALL, M.D., ROCHESTER, MINN.

(From the Mayo Foundation and the Department of Obstetrics and Gynecology, Mayo Clinic)

PYOMETRA was first recognized more than one hundred years ago when one of the first cases was reported by Clarke in 1851.<sup>1</sup> Fourteen additional reports appeared between then and 1920. About 1920, treatment of carcinoma of the uterine cervix by means of radiation therapy became fairly well established. Consequently, in the succeeding years numerous articles presented discussions and reports of the occurrence of pyometra as a result of obstruction of the uterine cervix by malignant growths, polyps, fibromyomas, calcareous concretions or fetal bones, and as a result of radiation therapy. Previous cautery, atrophy and stenosis of the cervix also were mentioned. Bland,<sup>2</sup> in 1929, noted that stenosis of the cervical canal was not necessarily present in all patients who developed pyometra. The condition has been noted when tumors were produced experimentally in animals. Two instances of pyometra in women occurred in association with the presence of excessive amounts of estrogens, one in the presence of granulosa-cell tumor and the other following the administration of large doses of estrogens. Investigation of the bacteria found in cases of pyometra was made by Carter<sup>3</sup> in 1942.

The records of 87 patients at the Mayo Clinic who developed pyometra, from 1917 through 1945, were available for study. The condition was found at operation in 46 instances, at necropsy in 6, and at diagnostic curettage in 25; in addition, 10 patients experienced the condition during, or shortly after, the administration of radium to the uterus.

The general clinical background of this group of patients will be presented first, followed by consideration of the pathologic aspects.

### Clinical Features

The incidence of pyometra is not high, the 87 cases discussed herein representing a little more than 1 in 10,000 female admissions to the Mayo Clinic. For the most part, patients with pyometra are of advanced age. The average age in cases reported in the literature was 53.2 years; however, our group averaged 58.1 years, the youngest being 23 and the oldest 88.

The majority of patients with pyometra have passed the menopause, as would be expected in this age group. The significance of the postmenopausal state has been considered by Meigs<sup>4</sup> and by Graham and Failla<sup>5</sup> who have pointed out that accompanying the advance of years the tone and contractility of the uterus dwindles so that it cannot empty itself. In 68 patients (78 per cent), the elapsed time since the last menstruation averaged 14.2 years, and, of these, 58

\*Abstract of thesis submitted by Dr. DeVoe to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Obstetrics and Gynecology.

had experienced a spontaneous menopause while in the remainder it followed surgical or radiologic procedures. One patient had been amenorrheic for 21 years after a premature permanent cessation of the menses at the age of 18. Nineteen patients had not experienced the menopause and of these, eight had menorrhagia or metrorrhagia and one had oligomenorrhea. Sixty-two patients had given birth to living children; twenty had never been pregnant and five had been pregnant once but had aborted.

Previous diseases which might be of significance rarely had been present. Six patients had experienced pelvic inflammatory disease, three cancer of the endometrium, and three vaginitis. Endometriosis, fibromyoma of the uterus, puerperal sepsis, and syphilis each appeared once in the past histories of this group.

The past surgical history contained certain items of more than passing interest. Gynecological operations in some form had been performed on 58 (67 per cent) of the 87 patients and surgical procedures involving the cervix in varying degrees had been performed on 23, or 26 per cent, of the 87 patients; these operations consisted of dilatation and curettage in twelve, cervical amputation in four, trachelorrhaphy in one, and minor procedures (cautery, biopsy, polypectomy) in six. Twenty-four patients had experienced some abdominal surgical procedures. A large number of procedures previously undertaken did not pertain to the pelvic viscera.

A significant number of these patients had been subjected to irradiation therapy. Indeed, pyometra is one of the complications which has plagued radium therapists from the beginning. Lammers<sup>6</sup> and Condamin<sup>7</sup> reported cases of this complication that occurred during the early experience in the treatment of cervical carcinoma with radium but maintained that radium was the best therapeutic agent. Pyometra developed in three of 116 patients treated by Gegouin<sup>8</sup> who expressed the belief that postirradiation stenosis of the cervical canal was the underlying factor. In sixteen of our patients who received previous irradiation therapy elsewhere, pyometra developed. It was difficult to ascertain, by the patient's account, the extent and direction of this treatment. In twelve, however, radium was placed in the cervix or uterine cavity in doses apparently ranging from a menopausal dose to "complete treatment." The pelvic organs of four patients were treated with roentgen rays. Ten additional patients underwent radium treatment at the clinic and pyometra developed during or shortly after treatment. In nine of these, treatment was for carcinoma of the cervix and in one it was administered to induce the menopause. In three of these women pyometra developed during treatment or less than a week after the last treatment and in seven it appeared from two to sixteen weeks subsequent to the final treatment.

The complaints and symptoms of these patients frequently appeared as a triad. Vaginal discharge was present in 42 patients, vaginal bleeding in 35, and abdominal pain in 40. Nine patients complained of a low back pain. Infertility, irregular menses, hot flushes, and rectal pain each were present once or twice. Many patients, of course, had no complaints referable to the pelvis. Vaginal discharge was present and described as foul in 24 cases, purulent in 23, bloody or bloody mixtures with other types in 16, and brown in 8. Discharges described as serous, profuse, green, irritating, and mucoid occurred infrequently. Fourteen patients had no discharge. Some patients had more than one type of discharge. Forty patients experienced abdominal pain. Twenty-two complained of lower abdominal pain, nine described menstrual-type pain and nine complained of pain in either the right or left lower quadrant. Relief of pain with the onset of vaginal discharge occurred in five patients.

The body temperature was above 99° F. in only 13 patients, the highest reading being 99.6° F.

The results of physical examination, particularly of the abdomen and pelvis, were helpful in a number of instances. Of the 87 patients, sixteen were found to have tenderness in the lower part of the abdomen, one of whom had semi-rigidity of the abdominal wall. Palpation of a tumor through the abdominal wall was possible in three patients.

Pelvic examination was performed on 71 patients.\* The uterus was enlarged in eighteen patients and a pelvic tumor was described in six. A mass in one or both sides of the pelvis was thought to be present in thirteen patients. Thus, in 37, or 52 per cent, of the 71 patients, enlargement of the uterus or a mass was noted. The cervix was absent in three patients, a cervical erosion was present in ten, a cervical scar in two, and an atrophic cervix in nine; in one patient a stem pessary was found in place.

Pyometra was the preoperative diagnosis in 21 of 71 patients. In the other 50 patients the results of examination led to a preoperative diagnosis of a number of conditions which in turn led to procedures through which pyometra was discovered. A pelvic tumor was diagnosed eleven times, cancer of the cervix five times, fibromyoma twice, menstrual irregularity nineteen times, and cancer of the fundus four times. Thirty-five patients were listed as having infrequently occurring conditions. The list of antemortem diagnoses of the patients who came to necropsy contained none of gynecologic interest.

### Pathologic Features

Studies of the gross and microscopic features of pyometra were possible in 52 cases in which the uterus was removed surgically or at necropsy. The Fallopian tubes were not present in all instances. The findings with regard to those patients upon whom a dilatation and curettage were performed will be noted later. In all patients evidence of the presence of pus in the uterus was found at the time of operation by the surgeon or immediately thereafter by the surgical pathologist.

The uteri from these patients varied greatly in size. The average weight of 50 uteri was 114.9 Gm., the lightest being 30 Gm. and the heaviest 187 gm. Two uteri contained multiple massive fibromyomas and hence were not considered in establishing the average weight; they weighed 530 and 390 Gm., respectively. The thickness of the uteri as measured at the fundus averaged 1.21 cm.; the thickest uterus measured 3.0 cm. and the thinnest 0.2 cm.

Many times pyometra was accompanied by other uterine pathologic lesions in the 52 cases in which the uterus was removed surgically. In this group there were 21 instances of benign uterine lesions; of these lesions fibromyomas numbered fourteen (27 per cent), endometrial polyps five (10 per cent), and adenomyosis two (4 per cent). Malignant lesions were present in eleven uteri (21 per cent), eight of which were endometrial carcinomas, one an extensive multicentric squamous-cell epithelioma of the endometrium, one a squamous-cell epithelioma which arose in the cervix and which involved the entire uterus, and one a squamous-cell endometrial metaplastic lesion. Concurrent pathologic conditions in other organs were of infrequent occurrence. There was one adenocarcinoma of the stomach, one adenocarcinoma of the ileum, and one diverticulum of the colon.

The status of the endometrium in this group of 52 patients was variable. In accordance with the average age of this group, a large number, 34 (65 per cent) exhibited an atrophic endometrium. A smaller number had an active

\*Pelvic examination was not done on the six patients who came to necropsy nor on the ten patients in whom pyometra developed during the course of radium therapy. In the "broken-dose" method of radium administration the cervix is probed prior to each treatment. When these patients complain of abdominal pain or vaginal discharge, probing the cervical canal is done and the diagnosis confirmed.



endometrium, four showing a late proliferative phase, three an early proliferative phase, and one a late differentiative phase. In three patients an extensive necrosis of the endometrium was present. As mentioned before, there were eleven instances of endometrial involvement by a malignant process; in four of these the lesion was endometrial adenocarcinoma, Grade II; in three endometrial adenocarcinoma, Grade I, in one a diffuse squamous-cell epithelioma, Grade III; in one a diffuse squamous-cell epithelioma, Grade II; in one an adenocarcinoma, Grade III; and in one a multicentric Grade III squamous-cell epithelioma of the endometrium.

The type of inflammation in the endometrium varied. Pus, of course, was present in all. The criteria used for acute inflammation was the presence of polymorphonuclear leucocytes and edema in the endometrium. A predominance of plasma cells was the principal criterion in cases of subacute inflammation, although eosinophilic polymorphonuclear leucocytes were often found. The presence of plasma cells in the uterus<sup>9</sup> is regarded by some as being indicative of chronic inflammation. Lymphocytes were the predominant cells found by us in chronic inflammation. On the basis of the foregoing criteria, five of the 52 patients had an acute purulent type of inflammation, with five others demonstrating, in addition, necrosis, giving a total of ten patients (19 per cent) with this type of inflammation. Twenty-nine (56 per cent) had a subacute purulent inflammation and ten had a chronic purulent inflammation. Tuberculosis was found in three uteri; tubercles with epithelioid cells, giant cells, and lymphocytes were present. When tubercles were discovered, special stains to demonstrate the presence of acid-fast organisms were tried, but none were found. However, the configuration seen scarcely allowed any other decision to be made since other granulomatous lesions which might be confused are extremely rare in the endometrium.

The principal feature noted in the myometrium was the presence or absence of fibrous change. The occurrence of fibrosis in the myometrium as well as in the cervix has been dealt with by Puxeddu<sup>10</sup> and Meigs.<sup>4</sup> In our group of 52 cases, marked fibrosis was present in 39 (75 per cent) and absent in 13 (25 per cent). In one the myometrium was diffusely infiltrated by a Grade III squamous-cell epithelioma. The number of uteri that revealed the presence of inflammation in the myometrium was surprisingly small; inflammation was not present in 24 (46 per cent), in twelve subacute inflammation was found, and in seven chronic inflammation was present. Four patients were found to have a subacute purulent myometritis, two an acute inflammation, and three acute purulent myometritis.

Accumulation of pus occurred both in uteri with and in those without a patent cervix. Twenty-four of the 52 uteri had a nonpatent cervix while the balance were not obstructed. Fibrosis of the cervix as a part of the general process in the uterus during the involutional age was present in 32 patients to a marked extent and nine showed fibrosis plus cystic cervicitis, giving a total of 41 (79 per cent) with increased fibrosis. Closure of the cervix as a result of atrophy, fibrosis of the circular structure, and subsequent adhesion has been demonstrated by Liegner,<sup>11</sup> Aza,<sup>12</sup> Alamanni,<sup>13</sup> and others (Gegouin,<sup>8</sup> Graham and Failla<sup>5</sup> and Puxeddu<sup>10</sup>). Other conditions of interest in the cervix were that three cervices had been amputated (plus one which had been removed post-operatively from the specimen) because of marked atrophy subsequent to radium treatment and 3 were the site of a Grade III squamous-cell epithelioma in which blockage occurred. This phenomenon has been recorded by Galabin,<sup>14</sup> Lewers,<sup>15</sup> Tate,<sup>16</sup> Oberndorfer,<sup>17</sup> and Roberts,<sup>18</sup> all of whose reports were published in early years; however, this condition, common in the past, is not so frequent now. The mechanism whereby pyometra occurs in the presence of an apparently patent cervix is conjectural; however, Tate,<sup>16</sup> Bland,<sup>2</sup> Maurizio,<sup>19</sup> and Guilhem

and Gouzy<sup>20</sup> maintained that a closed cervix is not essential. A physiologic retention may occur and increasing pressure may force exit. Varying types of inflammation were present in the cervix; seventeen of the 52 patients had subacute purulent inflammation, nine no inflammation, eight subacute inflammation, six chronic inflammation, nine acute purulent inflammation, two chronic purulent cervicitis, and one tuberculous cervicitis.

The total number of Fallopian tubes present on the 38 uteri having tubes was 72. The types of inflammation present in the tubes were as follows: no inflammation in 31, acute purulent inflammation in 13, subacute purulent inflammation in 21, chronic inflammation in four, and tuberculous reaction in three. Considering the ease with which it is possible for some inflammatory conditions to ascend into the tubes one would expect that the tubes would have exhibited the same type of inflammation as did the endometrium. Such was not the case. The type of inflammation in the 72 tubes corresponded to that in the endometrium in 22 instances (31 per cent) and was different in 50 instances. The three tuberculous endometria were all associated with tuberculous salpingitis.

Of the 25 patients upon whom a dilatation of the cervix and curettage of the uterus were performed, sixteen had a nonpatent cervix and in nine the status of the cervix was not given. In twelve of these 25 cases tissue was available for microscopic study; it was found that there were six cervical epitheliomas, four carcinomas of the endometrium, and two instances of only a purulent endometritis.

### Summary and Conclusions

The clinical and pathologic aspects of pyometra were studied in 87 patients, and the uteri of 52 were available for examination.

The average age of this group of 87 patients was 58.1 years, and in 78 per cent the last menstrual period had occurred 14.2 years before the onset of pyometra.

Gynecologic operations in some form had been performed on 58 (67 per cent) of the 87 patients, and in 23 (26 per cent) of the 87, a surgical procedure had been performed on the cervix. Twenty-one per cent of 71 patients, exclusive of the six who came to necropsy and the ten who received radium treatment at the clinic, had received irradiation therapy previously. Seven patients gave a history of endometrial or cervical malignancy.

The most prominent symptoms of pyometra were vaginal discharge, vaginal bleeding, and abdominal pain. Pyometra was not accompanied by fever.

Fifty-two per cent of 71 patients had a pelvic mass of one kind or another and 12 (17 per cent) had suspicious lesions of the cervix.

In 30 per cent of the patients who were treated surgically, pyometra was diagnosed preoperatively and in the remainder treatment was given for conditions which led to the discovery of pyometra.

Lesions of the uterus most frequently accompanying pyometra in the 52 cases in which the uterus was removed surgically were fibromyoma in 27 per cent, carcinoma in 21 per cent, endometrial polyps in 10 per cent, and adenomyosis in 4 per cent.

The endometrium was atrophic in 65 per cent of 52 cases in which the uterus was removed surgically. The types of inflammation present in the endometrium were as follows: subacute purulent inflammation in 56 per cent, acute purulent inflammation in 19 per cent, and chronic tuberculous purulent inflammation in

6 per cent. The myometrium was markedly fibrosed in 75 per cent of the 52 cases and the inflammation present in the endometrium did not gain access to the myometrium in 46 per cent of the uteri.

The cervix exhibited increased fibrosis in 79 per cent of the 52 patients. The cervical canals of 54 per cent of the uteri were patent and the type of inflammation present in the cervix was approximately the same as that present in the endometrium.

The Fallopian tubes showed all types of inflammation, the type being similar to that of the endometrium in 31 per cent of the cases. In 90 per cent the type of inflammation present in the right tube was similar to that in the left tube.

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## END RESULTS IN THE SURGICAL TREATMENT OF OVARIAN CANCER\*

A. W. DIDDLE, M.D., KNOXVILLE, TENN.

*(From the Department of Obstetrics and Gynecology, Southwestern Medical College,  
Dallas, Tex.)*

**T**HIS article concerns the treatment of patients with ovarian cancer in Dallas, Texas, from Dec. 31, 1935, to Jan. 1, 1947. It shows that surgical attack of the disease was frequently done without regard for its pathology. The effect on end results is considered. The method of study used was the same as described in a previous report.<sup>5</sup> The survey was completed in May, 1948.

### Material

Records of 294 women with a histologic diagnosis of ovarian cancer, and 20 others with a feminizing tumor of the ovary were reviewed. The feminizing tumors were considered separately for the reason that it was usually impossible to ascertain histologically whether or not they were malignant. Clinically, several of them proved to be cancerous.

To evaluate treatment of ovarian cancer, the tumors were divided into four clinical groups according to the modification of Heyman's classification made by Kerr and Einstein.<sup>10</sup> Among Group I the primary tumor and all visible cancer tissue was excised. Among Group II part or all of the primary tumor was removed but in every instance either some tumor was left, there was ascites, or the tumor content was spilled during removal. Group III included cancers recurring after removal or after irradiation treatment and Group IV consisted of the inoperable tumors.

### Subjects

Two-thirds of the patients were residents of Dallas County. The other one-third lived outside of Dallas County and came from other parts of Texas, Arkansas, Oklahoma, New Mexico, and Louisiana to Dallas for treatment.

The age of the women with ovarian cancer ranged from 16 to 87, with an average of 50 years. Two-thirds of them were over 45. Twelve, or 4 per cent, were under 30 years old.

### Symptoms

The usual symptoms of ovarian malignancy were abdominal tumor and pain. The average delay from the onset of symptoms to the time a correct diagnosis was made averaged 8.5 months. There was no apparent relation between the duration of symptoms and the extent of the disease. It was impossible to ascertain the amount of delay attributable to patient and to doctor but most of it was believed the fault of the patient.

\*Aided by a grant from the Texas Division of the American Cancer Society.



### Pathology

The majority of ovarian tumors were primary in the ovary. Less than 8 per cent were metastatic, arising in order of frequency from the endometrium, colon, stomach, sigmoid, kidney, and cervix. Three of seven Krukenberg tumors were primary in the stomach, while the origin of the other four was unknown.

The histologic types of ovarian cancer are given in Table I and the clinical grade among patients traced three and five years is shown in Table II. Note, the specific histologic type was frequently not given. Most of the cystic tumors contained papillations. Over one-half of the 90 patients subjected to bilateral oophorectomy had cancer in both ovaries. One-seventh of the 122 women with one or both Fallopian tubes excised had metastases to at least one tube. Over one-third of the 46 women hysterectomized had spread of the malignant tumor to the uterine wall or into the uterine lumen. One-sixth of all the patients had extrapelvic metastases, usually to the omentum, and in nearly one-third of the 187 laparotomized other than for biopsy, the cancer had broken through the ovarian capsule. Spill of the tumor contents occurred among one-ninth of the women oophorectomized. Possibly some of the recurrences in these patients can be attributed to this technical misadventure. Grossly, all of the cancer was removed in only one out of 21 women.

TABLE I. HISTOLOGIC TYPES OF OVARIAN CANCER AND FEMINIZING OVARIAN TUMORS

HISTOLOGY	NUMBER
Adenocarcinoma, variety unspecified	144
"Ovarian cancer" type unspecified	37
Pseudomucinous cystadenocarcinoma	35
Serous cystadenocarcinoma	27
Metastatic, exclusive of Krukenberg tumors	16
Other*	15
Feminizing (granulosa cell 18, theca cell 2)	20

\*Krukenberg 7, epidermoid 5, sarcoma 1, dysgerminoma 1, embryonal 1.

TABLE II. SURVIVAL RATES

CLINICAL GROUP	FIVE YEAR (1936-1941)			THREE YEAR (1942-1943)		
	TOTAL	NUMBER LIVING	PER CENT	TOTAL	NUMBER LIVING	PER CENT
I	20	15	80.0	12	10	84.4
II	45	5	11.1	31	4	12.9
III	3	2	66.6	1	0	0.0
IV	32	0	0.0	23	3	13.0
Unclassified	4	1	25.0	5	1	20.0
Total	108	23	21.3	74	18	24.4

### Treatment

The various surgical measures used to treat ovarian cancer are given in Table III. Only seven women in the entire series of 294 received what may be adjudged an adequate operation for ovarian cancer. In other words, only one in 42 women had a known bilateral salpingo-oophorectomy and total hysterectomy! One in fourteen women was laparotomized for recurrence of the tumor, found usually in the remaining ovary. Where an ovarian tumor was excised and a few days later reported to be malignant, the abdomen was seldom reopened to remove the other adnexus and uterus. The omentum was seldom removed and then only partially.

Reliable information regarding irradiation was available for only about one-half of the patients. These received x-ray to the pelvis or abdomen postoperatively.

TABLE III. TREATMENT

TREATMENT	NUMBER
Exploratory laparotomy and biopsy	68
Unilateral oophorectomy	51
Bilateral oophorectomy	44
Unilateral salpingo-oophorectomy	30
Type of surgical operation unspecified	30
Subtotal hysterectomy and bilateral salpingo-oophorectomy	25
Bilateral salpingectomy and unilateral oophorectomy	12
Total hysterectomy and bilateral salpingo-oophorectomy	7
Subtotal hysterectomy and unilateral salpingo-oophorectomy	7
Abdominal paracentesis	5
Subtotal hysterectomy, bilateral salpingectomy, and unilateral oophorectomy	3
Total hysterectomy and unilateral salpingo-oophorectomy	2
Unilateral oophorectomy and bilateral salpingectomy	2
Bilateral oophorectomy and unilateral salpingectomy	1
Total hysterectomy and unilateral oophorectomy	1
Subtotal hysterectomy and unilateral oophorectomy	1
Died without operation, autopsied	5
Total	294

### Survival Rates

The survival rates for the 80 per cent of patients traced with ovarian cancer are given in Table II in relationship to the modified Heyman Classification. Spill of the tumor during its removal apparently decreased the chance for survival. In other words, aspiration and deflation of a tumor to facilitate removal are condemned. All women with sarcoma, epidermoid carcinoma, Krukenberg tumor, and dysgerminoma of the ovary died in less than four years after diagnosis. Four of five women with ascites and nearly all with palpable implants in the cul-de-sac were dead or had a recurrence within two years after a diagnosis of cancer was made. Since there were few patients with any one grade of tumor treated by any one method, it was impossible to evaluate properly surgical and irradiation treatment.

### Complications

More than one-half of the patients with ovarian cancer had known complications secondary to the disease or treatment, Table IV. The majority of women with ascites had one or more paracenteses. Seventeen with metastases to the bowel ultimately had an intestinal obstruction necessitating surgical intervention.

TABLE IV. COMPLICATIONS

COMPLICATION	NO. CASES
Peritoneal metastases (56 with ascites)	105
Extension to bowel	46
To lymph nodes; cervical 7; inguinal 7; other 3	17
Pulmonary metastases	7
Metastases to bone	4
Metastases to abdominal scar	4
Urinary tract obstruction	4
Metastases to iliac vessels	4
Total	191*

\*Among 168 patients.

### Feminizing Tumors

Several women with feminizing tumors of the ovary noted abnormal vaginal bleeding for over one year and in a few instances for as long as five to ten years

prior to institution of treatment. Originally some of these tumors were considered to be sarcomas but on further study they were interpreted to be granulosa cell tumors. There were isolated instances where these tumors metastasized to omentum, peritoneum, Fallopian tube, scalp, and bone marrow.

Approximately an equal number of women laparotomized for feminizing neoplasms had removal either of one or both ovaries. Postoperative irradiation was seldom used. Six of thirteen women traced were dead within seven years, and two of four patients under 30 years of age died of the disease. It was apparent that the surgical procedure of choice for the older women with feminizing tumors included total removal of the uterus, ovaries, and tubes. The justification for doing less radical procedures in young patients as recommended by Hodgson, Dockerty, and Mussey<sup>9</sup> is questioned because two of four women under 30 years old died of the disease.

### Comment

Undoubtedly the great waste of time from onset of first symptoms to beginning treatment, and the use of improper operative treatment contributed to poor end results. It was apparent that many physicians did not understand the pathology of the disease. For the foregoing reasons, a brief discussion of the pathology and treatment of ovarian cancer is given.

Many ovarian malignancies arise within previously benign neoplasms.<sup>19</sup> The onset of the malignant change is insidious, so that the tumor is usually in an advanced stage of growth before a diagnosis is made. Ovarian cancers not uncommonly involve both ovaries. The tumor usually spreads by direct extension to the peritoneum, omentum, or tube. Less often metastases occur to the Fallopian tube by the lymphatics or veins and then to the uterus.<sup>4, 11, 18, 22</sup> It is obvious that total hysterectomy and bilateral salpingo-oophorectomy are the minimum acceptable surgical procedure for operable ovarian cancer.<sup>1, 3, 4, 6, 8, 10, 14, 15, 16, 18, 21</sup> In addition, Meigs<sup>14</sup> and Pemberton<sup>18</sup> strongly advise removal of the omentum. To the contrary, Baer<sup>2</sup> opposes its removal routinely for the reason that once tumor has spread to omentum it usually has invaded other extragenital organs or the peritoneum. Death from ovarian cancer commonly results from intestinal obstruction produced by peritoneal implants or invasion of other viscera, not from omental metastases. As previously mentioned, aspiration of ovarian cysts decreases the survival rate and is, therefore, condemned. On the other hand, drainage of very large ovarian cysts may be the only possible method of permitting subsequent removal without patient fatality. If done, a small midline incision is made and aspiration done under direct vision. The trocar wound is closed with a purse-string suture to prevent leakage.<sup>20</sup>

The normal ovary is removed unnecessarily often. In contrast, this survey revealed a tendency to conserve ovarian tissue in the presence of a malignant tumor of the ovary. Such a policy should be considered only in a young patient where the involved ovary is a freely movable, small cystic mass.<sup>15</sup> On the contrary, Helsel<sup>8</sup> is of the opinion that age should not be a factor in the treatment of ovarian malignancy. Ordinarily, if an ovary is removed, especially in women of menopausal age, and found to contain cancer, it is negligence if the other ovary, tubes, and uterus are not removed within a few weeks.<sup>14, 15</sup> All tumors taken out singly should be opened at the operating table to determine if they are malignant before the abdomen is closed. If the surgeon feels unqualified to pass on the gross specimen, he should consult the hospital pathologist. When ovarian cancer is found, as much of the tumor as possible should be removed with due regard to the length of anesthesia, blood loss, and shock. The more cancerous tissue excised, the more favorable the outcome, particularly if roentgen treatment is to be used.<sup>6</sup> Maun and Dunning<sup>12</sup> state that removing a portion of a

tumor from experimental animals results in an increased survival rate presumably due to reduction in the number of cells available for growth. They are of the opinion this principle holds clinically.

Clinically the problem commonly arises as to whether or not an ovarian tumor is of the physiologic or neoplastic variety. Movable, cystic tumors 5 to 6 cm. or less in diameter in patients in the reproductive period of life are usually physiologic cysts. However, such tumors bear watching and if they do not regress, or instead become larger, an exploratory laparotomy is indicated.<sup>16</sup>

The value of irradiation in the treatment of ovarian cancer is difficult to judge because reporting of data is not uniform.<sup>22</sup> It apparently cuts down the formation of ascites and slows the growth of implants. Given postoperatively, life is occasionally prolonged.<sup>1, 7, 8, 10, 16</sup> In selected studies, total hysterectomy and bilateral salpingo-oophorectomy combined with postoperative irradiation have effected five-year survival rates of 35 to 40 per cent. On the contrary, Martin<sup>13</sup> seriously questions the value of x-ray postoperatively to prolong life. Baer,<sup>2</sup> Parks,<sup>17</sup> and the writer have observed that preoperative irradiation, in a few instances, made inoperable ovarian tumors operable. Kerr and Einstein<sup>10</sup> rightly condemn this procedure unless a histologic diagnosis is made beforehand. To give x-ray solely on a clinical diagnosis too often leads to castration of the patient for a benign lesion.

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## ON THE VALIDITY OF THE HYPEREMIA METHOD FOR DETERMINING OVULATION TIME IN WOMEN\*

LOUIS LEVIN, PH.D., C. L. BUXTON, M.D., AND E. T. ENGLE, PH.D.  
NEW YORK, N. Y.

*(From the Departments of Anatomy and Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University)*

THE search for a simple and reliable means of determining the time of human ovulation has led to the proposal of a variety of techniques. "Mittelschmerz," spotting, gonadotrophin excretion, changes in electrical potential and in basal body temperature, vaginal smears, and endometrial biopsies have been among the criteria proposed. One of the most recent suggestions is that of Farris,<sup>1</sup> who has adapted a technique previously presented by others<sup>2, 3</sup> as a test for detection of early pregnancy. The test depends on determining the extent of the hyperemic response of the immature rat ovary two hours after injection of 2 ml. of morning urine. A positive indication of ovulation is defined on the basis of hyperemia of a specified degree and quality as determined by comparison of the test animal's ovaries to a standard color chart. It is further stated that in the normal reaction, the subject's urine must produce the hyperemic response for at least three successive days (later revised<sup>4</sup> to four or more days).

In the original report,<sup>1</sup> Farris states that by use of this method he has correctly predicted ovulation time in a number of women, the criterion for correctness of the prediction being conception resulting from timed coitus or artificial insemination. Furthermore, the prediction of the time of ovulation in seven monkeys has been verified<sup>5</sup> by finding the corpus luteum of ovulation at examination of the ovaries at laparotomy.

Because of the great potential value of the technique, an attempt has been made in this laboratory to evaluate the hyperemia test in the prediction of ovulation. The published technique<sup>1, 6</sup> was followed exactly except that for the examination of the ovaries of the test rats natural north light or light from a battery of fluorescent lamps was substituted for the special lamp suggested. The test ovaries were compared to the Munsell Color Chart as nearly as possible as described by Farris. In addition, positive and negative controls were included in each group of test animals. The negative controls consisted of un-injected rats of the same age (usually littermates) as those injected with test urines. The positive controls were similar rats injected with 2 ml. of urine collected from patients known to be in the first trimester of pregnancy.

The test urines were morning specimens furnished daily throughout a complete cycle by each of four normal women volunteers. Daily basal body

\*Aided by a grant recommended by the Committee on Growth of the National Research Council to the American Cancer Society and administered by E. T. Engle and Howard C. Taylor, Jr.

temperatures were taken by each of these four subjects so as to compare this criterion of ovulation to the hyperemia test. In so far as could be determined all four subjects were clinically normal. Three had become successfully pregnant one or more times without difficulty in conception. The fourth subject was a 30-year-old nullipara whose menstrual cycle was regular and who presented a completely normal history.

In addition, data were obtained from three selected patients who were to be subjected to pelvic repair surgery of nonendocrine significance. The surgical procedures were timed to occur on the day after ovulation as judged by the sudden rise in basal body temperature. In these cases as many morning urine samples as possible, immediately preceding the supposed time of ovulation, were obtained and tested by the Farris technique. It is to be noted that in two of these three subjects a freshly ovulated follicle developing into a corpus luteum was found.

Examination of the data (Fig. 1) indicates that our experience with the method has not been encouraging. None of our subjects, with the possible exception of L. S., yielded a normal or near normal ovulatory pattern according to the specifications of Farris. If this test is in reality dependable, the only interpretation is that all our subjects were abnormal with respect to ovulatory pattern. This does not seem likely because, as mentioned above, all these women were gynecologically and endocrinologically normal in so far as could be judged clinically and by past performance. Certainly, in the two subjects whose ovaries contained newly developing corpora lutea, the Farris test did not yield a "normal" reaction.

In the light of our lack of success with this method it is pertinent critically to re-examine the claims of Farris. In his first paper<sup>1</sup> he reports that a positive response on less than 3 successive days is to be considered abnormal. Yet in his chart of 52 "normal" cycles, 19 show positive responses on 2 or less consecutive days. Likewise, 13 of the 36 "abnormal" cycles were positive on 2 consecutive days. It is difficult to perceive from the data how these 19 "normal" cycles differed from the 13 "abnormal" ones. Likewise, the reasons for the arbitrary three days (later revised to four days) of required positive reaction is not readily understandable, especially in view of the fact that Farris<sup>6</sup> has also obtained positive reactions with pre- and postcoital urines of men and of women not ovulating at the time of urine collection.

Farris<sup>1</sup> reports that of eleven women showing normal ovulatory patterns and artificially inseminated on the day indicated by the hyperemia test, eight became pregnant, a successful prediction in 73 per cent. In a subsequent report, however, Murphy and Farris<sup>4</sup> outline results obtained by coitus or by artificial insemination timed in accordance to the hyperemia test. Sixty-six attempts in thirty-three cycles of ten women are detailed. All ten subjects became pregnant, one of them twice, a total of eleven successful predictions. Actually, however, the proportion of successes was only 33 per cent since in only eleven of the thirty-three cycles did conception occur. It is presumed that these eleven successes include the eight mentioned in the earlier publication. It is also to be noted that in many of the test cycles, coitus was repeated on a number of successive days at approximately the middle of the cycle rather than on the one day predicted by the test. The percentage of successful conceptions, therefore, loses a large measure of its significance for with repeated coitus during each cycle a 33 per cent incidence is not strikingly higher than that obtained without prediction of ovulation by special methods.

Furthermore, the significance of five of the eleven successes appears to be doubtful due to extenuating circumstances such as the substitution of a sperm donor for an infertile husband (Case 1), repair of closed fimbria (Case 2),

husband of doubtful or fluctuating fertility (Cases 4 and 6), coincident treatment of husband with gonadotrophic preparations (Case 6), and a relatively infertile husband plus suspected opening of a blocked tube (Case 10). Two other cases (5 and 7) had previously been pregnant and in these two cases, three pregnancies resulted from four coital attempts.

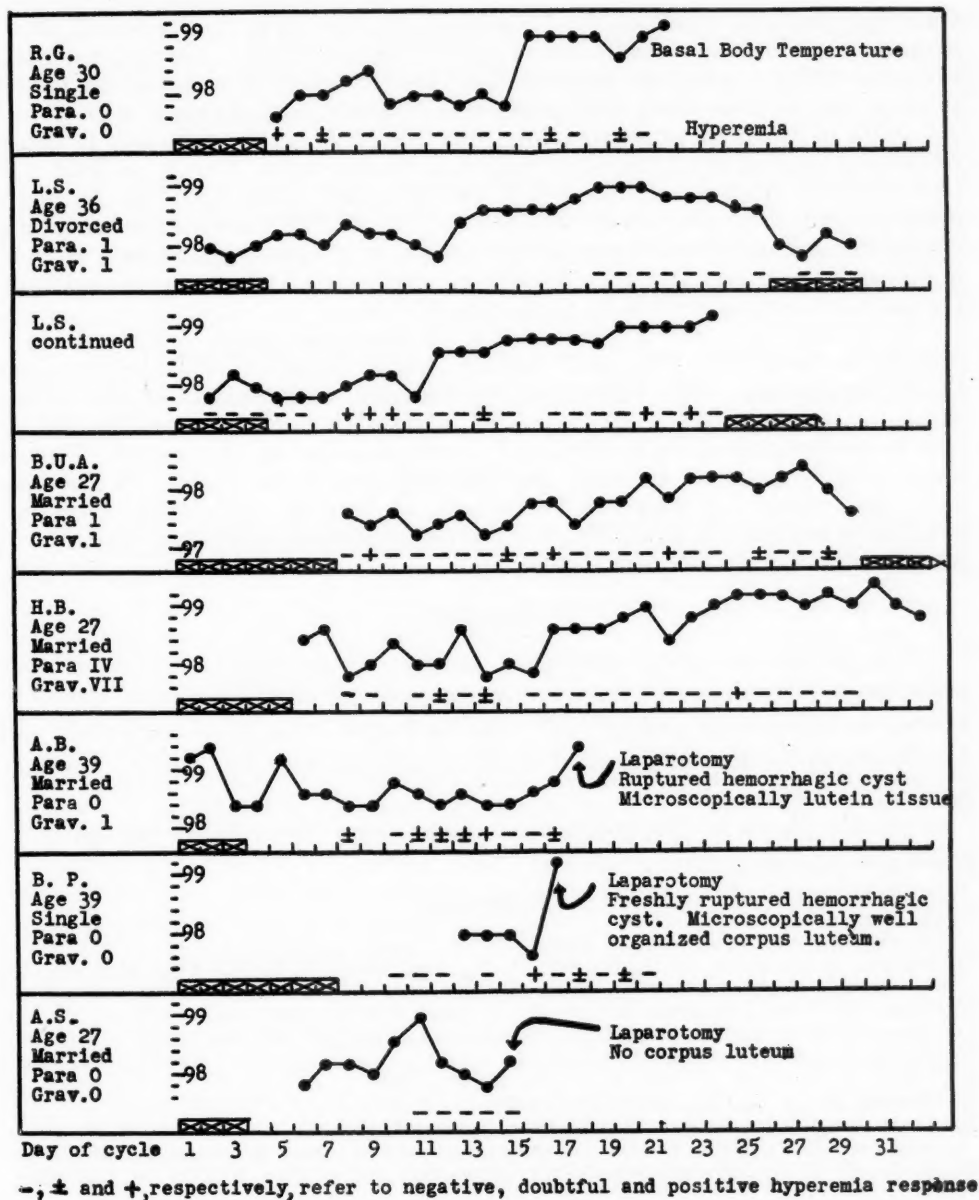


Fig. 1.

Cases 4 and 10 are of further interest. These two subjects practiced coitus during seventeen cycles as advised on the basis of the ovulation test. During the final cycle in each case conception occurred. Adequate explanation for the

fifteen failures in these two cases is lacking. Possible infertility of the husband due to previous coital attempts is suggested (but not proved) as the reason for five of the failures. No explanation at all is given for five other failures.

Thus, even the cases cited by Murphy and Farris do not all clearly support their thesis and the incidence of success based on the hyperemia test may actually be as low as 18 per cent or less.

Another puzzling aspect of the test which requires some thought is the statement that the cause of the "positive" hyperemia is the increased titer of urinary gonadotrophin immediately preceding ovulation. Farris presents no evidence which places the responsibility for the positive response on gonadotrophin but he does state that a positive response was obtained with 3 to 25 rat units of purified gonadotrophin. On the basis of these figures it may be calculated that at the time of ovulation a woman must excrete at least 1,500 to 12,500 rat units of gonadotrophin per 24 hours. This figure is enormously greater than any previously reported<sup>7, 8, 9, 10, and others</sup> and approaches more closely the values hitherto associated with early pregnancy. Indeed, if Farris is correct on this point we may discard as erroneous all hitherto reported figures for gonadotrophin excretion by nonpregnant women.

It is conceded that a criterion for determining human ovulatory time is difficult to establish. The only certain means of proof is by appropriately timed laparotomy with subsequent microscopic examination of the ovaries. Evidence based on fertile copulation or insemination is suggestive but not conclusive particularly when incidence of success is as low as 33 per cent. Furthermore, it must be borne in mind that nonovulation in the absence of the "positive" hyperemia test also still remains to be proved. Therefore, until more conclusive evidence is available, the Farris hyperemia test must remain as an interesting but unproved suggestion.

### Summary

The Farris rat ovary hyperemia test for determination of time of human ovulation has been used in three human subjects followed by examination of the ovaries at laparotomy and in four subjects known from previous history to be fertile and gynecologically normal. In none of these was the specified "normal" hyperemia reaction obtained.

Certain flaws in the conclusions upon which the validity of the test is based are discussed.

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## THE OBSTETRIC USE AND EFFECT ON FETAL RESPIRATION OF NISENTIL

FRED B. HAPKE, M.D., AND ALLAN C. BARNES, M.D., COLUMBUS, OHIO

*(From the Department of Gynecology and Obstetrics of the Ohio State University College of Medicine)*

THE substituted piperidene products have been thoroughly investigated as narcotic agents, and several modifications of the piperidene nucleus have been found highly satisfactory.<sup>1-6</sup> Since it is almost inevitable that any new pain-relieving drug which is introduced will be applied to obstetric analgesia, it becomes imperative to know the effect on the fetus of such drugs when administered during the course of labor. The present report records the effect on the fetal respirations of the 4-phenyl-4-acyloxy-piperidine, Nisentil\* administered to the mother prior to delivery, together with observations on its pain-relieving value in obstetrics.

### Procedure

Initial observations were carried out on five hundred patients to determine the proper dosage range for obstetric use and to evaluate the pain-relieving quality of the drug during labor. This evaluation was made by objective observation of the patient in labor and by postpartum questioning. In 40 mg. doses administered hypodermically, Nisentil has proved satisfactory for obstetric use. The duration of action of such a dose is about two hours, and characteristically the patients become drowsy, manifesting restlessness with each contraction. The progress of labor has not been significantly delayed. In a few women nystagmus has been noted, and mild mental confusion is not infrequent. Supplementary medication with the barbiturates or with scopolamine has been found to be necessary much less frequently, and in smaller doses. No untoward side reactions have been observed. Thirty-two of the five hundred patients were listed as receiving only moderate relief, seventeen "poor" to "none," while the remaining patients (90 per cent) were variously listed as having received "satisfactory," "good," or "excellent" results. The degree of pain relief was less than with 100 mg. of meperidine hydrochloride (Demerol) plus a barbiturate, and the amnesia was not as great as with meperidine hydrochloride and scopolamine combinations. Greater patient cooperation was retained, however, and over 70 per cent of these women were carried through the first stage in adequate comfort without additional medications.

### Fetal Respiratory Effect

*Method of Study.*—The time intervals between delivery of the head and (a) the first respiration and (b) the first lusty cry were carefully recorded, while an effort was made to eliminate or to standardize all factors other than the drug under study which might depress fetal respirations.<sup>7</sup> The pain of the labor was controlled either by caudal or by saddle block spinal anesthesia, obviating the use of systemic anesthetics or other analgesic drugs. All cases

\*Supplied by the Hoffman-LaRoche Company, Nutley, N. J.

were concluded by outlet forceps after rotation of the head was complete. Patients were eliminated from the study in whom unanticipated obstetric difficulties were encountered which could influence the initial breathing time (difficult outlet forceps, prolonged second stage, evidence on postdelivery inspection of marginal separation of the placenta, etc.). It was felt that any other factors which might affect the initiation of respirations would be balanced by the size of the series, and under such controlled circumstances the most important single influence on the baby's crying time was the drug under study, an influence which was accentuated by using maximum doses throughout and by administering the drug just prior to delivery (one to two hours in most cases).

**Results.**—Three hundred eleven cases were found acceptable for study in this manner. These were divided into one hundred eighty-one patients who had received Nisentil and one hundred thirty patients who served as controls. The control cases were further subdivided into the following groups: 38 who received no medications, 32 who received Methadon, and 60 who received Demerol.

As revealed by the breathing and crying times, Nisentil is not a serious fetal depressant. Of the drugs tested, Methadon<sup>7</sup> produced a definite and at times very marked delay in fetal respiration, while Demerol and Nisentil both tended to approach the unmedicated group in promptness of breathing and crying. In two of the Nisentil cases, it was noted that after immediate establishment of breathing the babies became sleepy and required mild physical stimulation; both cases had received multiple doses of the drug. In general, however, little depressant effect could be traced to Nisentil used alone, and if administered two hours or more prior to delivery no significant effect at all was observed.

In an effort to determine what dosage level would be required to produce definite depression of the fetus, and to assess a cumulative effect, if any, disproportionately large amounts of Nisentil were administered to an additional group of thirty patients. Fetal respiratory depression became evident on the administration at regular two-hour intervals of five consecutive 40-mg. doses. That this amount would be required frequently is highly unlikely, but it may well indicate that, as is true with meperidine hydrochloride, continued administration throughout a protracted first stage could have a deleterious effect on fetal respirations.

### Discussion

It would be absurd to maintain that any systemic narcotic now known is totally without effect on the fetus. All have a depressant reaction of some degree, as any careful study will indicate. But it is possible to measure such depression, and to select drugs which will provide a maximum of pain relief for a minimum of depressant effect.

One of the benefits in this respect derived from Nisentil as we have used it has been the fact that when employed in 40 mg. doses concomitant medication with other drugs has become less necessary. Nembutal has rarely been indicated and if scopolamine has been employed its dosage has been low (0.2 mg.). The drug repeated at 2- to 2½-hour intervals has proved satisfactory to carry more than 90 per cent of these patients up to the time saddle block spinal has been established. There has been a significant freedom from side reactions, either observed at the time or reported subsequently.

### Conclusion

The hypodermic administration of Nisentil in 40 mg. doses provided adequate pain relief in over 90 per cent of the five hundred patients who received it during labor.

Under carefully controlled conditions for study there was little evidence of fetal respiratory depression, and if the last dose was administered two hours or more prior to delivery, no significant effect on the fetus could be determined at all. Nisentil should prove a satisfactory adjunct to the armamentarium of pain-relieving drugs for obstetric use.

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## FATAL OBSTETRIC SHOCK FROM PULMONARY EMBOLI OF AMNIOTIC FLUID

PAUL E. STEINER, M.D., CLARENCE C. LUSHBAUGH, M.D., AND  
H. A. FRANK, M.D., CHICAGO, ILL.

*(From the Department of Pathology, University of Chicago)*

**I**N 1941 a series of eight cases of unexpected, sudden deaths in obstetric shock was described.<sup>1</sup> The necropsy finding common to all was the presence of numerous foreign bodies in the small pulmonary arteries, arterioles, and capillaries. These were regarded as emboli composed of the particulate components of amniotic fluid, including vernix caseosa (desquamated squamous epithelium and sebaceous material) and, in some cases, meconium (mucus and desquamated epithelial cells). Emboli composed of lanugo hair were later described.<sup>2</sup> These foreign materials were absent in the lungs of control interpartum cases. The clinical picture was that of sudden onset during labor or soon thereafter of strong or violent uterine contractions, restlessness, dyspnea, cough, rapid pulse, fall in blood pressure, cyanosis, etc., characteristic of shock. In four cases the pulmonary emboli were the most probable explanation for shock and death. In two cases there was, in addition, uterine hemorrhage and in two cases there were other important lesions as well.

It was possible to produce a similar clinical and pathological picture in rabbits and dogs by the intravenous injection of meconium and of unfiltered amniotic fluid, but not with filtered amniotic fluid. It is well known that in man and animals extensive showers of small particulate materials to the lungs can cause a shock reaction which may be fatal. This picture which is similar to if not identical with that of anaphylactoid shock is further characterized by widespread and, to a certain extent, species specific changes in the functional state of the smooth muscle of various body systems. It was believed that in some cases death was due to the pulmonary embolism. It was speculated that in other cases the state of shock might have caused uterine atony with resultant hemorrhage which together with the shock itself might have caused death. Finally, it was believed that the violent uterine contractions, which sometimes characterized the early stages of the condition, might have led to uterine rupture seen in one case, and in this way contributed, together with the shock of embolism, to death.

Later, two additional examples of the disease were described.<sup>2</sup> In these cases the embolism was not the cause of death, but they illustrated several additional features including the late histologic reaction to the emboli (previously seen only in the experimental animals), lanugo hair as emboli, and mild embolism in the absence of labor pains.

A number of confirmatory reports have since appeared. These include papers by Hemmings (one case), Goodof (one case), Gross and Benz (three cases), Wyatt and Goldenberg (one case), Jennings and Stofer (one case), Barron and co-workers (two cases), and Watkins (one case). Their clinical histories are typical and their photomicrographs illustrate the characteristic



emboli in pulmonary vessels. Jennings and Stofer have reviewed most of these cases. That they represent only a portion of the recognized cases is known to us as we have seen others in consultation, and there are references on record to cases which are incompletely reported such as that of Burt and of Nicholson. As was anticipated in the first paper, sublethal forms of what are probably this condition have been recognized pathologically,<sup>2</sup> and also clinically by Seltzer and Schuman and by us.

An outstanding new contribution was that of Gross and Benz who showed how the disease may sometimes be diagnosed in suspicious cases where necropsy examination is unobtainable by centrifugation of blood aspirated from the right ventricle. The embolic material, if present, separates as a special layer. Failure to find the emboli in the centrifugate would not exclude this diagnosis because the material might not have been present in heart blood at the moment that circulation stopped.

A new case which is perhaps the clearest and most dramatic in our series and which presents several new features is herewith presented. The time between clinical onset and death was exceedingly short (less than fifteen minutes). The membranes had not ruptured to the exterior. There was no hemorrhage whatever.

### Case Report

N. F. (No. 5772), a white woman, aged 44 years, was at term in her fourth pregnancy, which had been uneventful. She had had no symptoms suggestive of toxemia. The urine was free of albumin, the blood pressure had not been over 130 systolic, and the pulse was never counted over 76. Her youngest child was 19 years of age. After fourteen hours in mild to moderately severe labor the cervix was slightly dilated. The membranes had not ruptured. She was in good condition; she was up and walking around her room. Three minutes later she had a slight convulsion, turned cyanotic, and died within a few minutes despite measures for resuscitation, including Adrenalin, Coramine, and oxygen.

At necropsy, performed twelve hours after death by Dr. H. A. Frank, a normal term fetus weighing 3,320 grams was found within apparently intact membranes. The placenta was not detached. There was no evidence of hemorrhage, internal or external. The 310 gram heart showed dilatation of the right chambers. The lungs weighed 360 and 330 grams; they showed only a slight edema. There was no foreign body or other abnormality in the respiratory tract. The other viscera were essentially normal for a woman in late pregnancy.

The important microscopic findings were confined to the lungs and uterus. In addition to a slight pulmonary edema, bodies were found in many small pulmonary arteries, arterioles, and capillaries. They resembled epithelial squames, masses of mucus, masses of amorphous granular material resembling the sebaceous material in vernix caseosa, and leucocytes. These materials were found in the veins of the parauterine plexus and in the wall of the uterus itself (Figs. 1, 2, and 3).

### Comment

In many respects this case was typical of those previously described. An elderly multipara of short stocky habitus (length 5 feet, 1 inch; weight 157 pounds), after an uneventful pregnancy, suddenly and unexpectedly during labor went into collapse and died within fifteen minutes. The gross findings at necropsy were negative except for a dilated right heart and a slight pulmonary edema. All microscopic sections of lung taken at random, however, showed extensive embolization of small blood vessels by the particulate materials found in amniotic fluid.

The time which elapsed between the onset of symptoms and death, less than fifteen minutes, was the shortest in our experience, although others have reported such cases. Despite the short duration, however, there were many leucocytes

about and within emboli. This is interpreted as signifying either that the mobilization of leucocytes is extraordinarily fast, or that the emboli enmesh leucocytes in passing through the blood, or that the embolism had preceded, at least in part, the clinical onset of symptoms by some time. At necropsy in this case a rare opportunity was overlooked to demonstrate the actual site of passage of the amniotic fluid from the membranes into the maternal circulation by special methods, using pressure and dyes. A rent was not visible on casual examination.

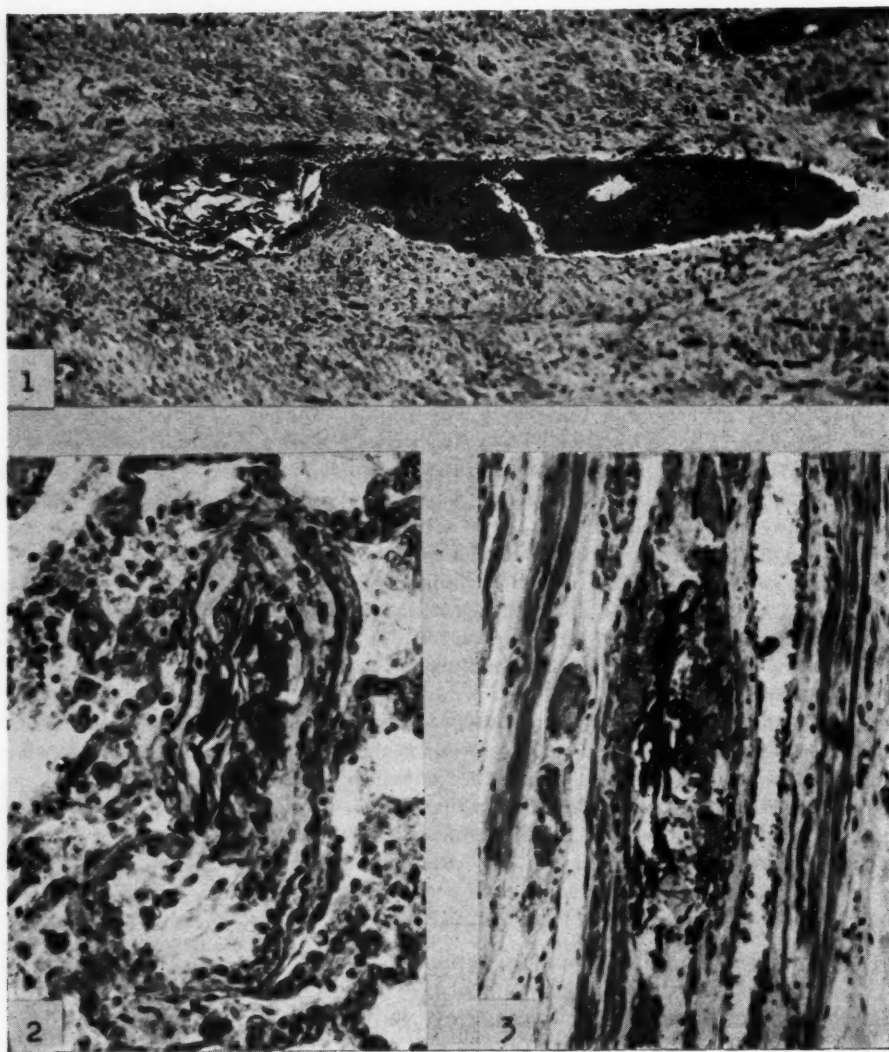


Fig. 1.—Uterine vein showing an embolus composed of epithelial squames, a little mucus, and sebaceous material at its left end. ( $\times 80$ .)

Fig. 2.—Dilated pulmonary arteriole filled by an embolus. It consists of epithelial squames enclosed by mucus which contains a few leucocytes (seen best at the lower end). ( $\times 250$ .)

Fig. 3.—Uterine vein showing an embolus of mixed composition but chiefly epithelial debris. ( $\times 140$ .)

In a previous publication the incidence of this form of obstetrical death was estimated to be about 1 in 8,000 confinements. This figure was based on the observation of three cases in the first 24,000 deliveries at the new Chicago Lying-in Hospital. This figure is probably too high because at that hospital since the time of making the estimation given here, there have been no further cases in over 26,000 additional deliveries. The case reported here came from another hospital. The exact incidence is hard to determine because the cases may occur at irregular intervals as witness the three seen by Gross and Benz within one year.

We stated that in our material this was the commonest cause of death during labor or in the first few hours of the puerperium.<sup>1</sup> In view of these observations it is difficult to understand the statement of Sheehan who in 147 deaths from obstetrical shock in a period of ten years recognized no examples of this condition. He stated that sections of lungs which he examined showed no emboli of amniotic fluid but failed to state how many lungs he had adequately examined. The experience of Scott who in eighty-two obstetrical deaths did not see this condition is also difficult to explain other than on the probable basis of failure to make the necessary histological examination of the lungs. In Feeney's learned lecture on shock in obstetrics there is no mention of cases due to this form of embolism although his second class is probably of this type. Johnson, in an excellent discussion of sudden death in obstetrics, fails to mention the possibility of this form of embolism; a review of microscopic sections of lungs in some of his obscure cases would probably disclose the characteristic emboli.

Fatal maternal embolism by the particulate contents of amniotic fluid is now a well-established cause of death. Because this label could be used to mask the cause of many types of unexpected death in parturition, this diagnosis should be accepted only when verified by the finding of particulate amniotic contents in the heart or lungs either by cardiac puncture or necropsy. On the other hand, in all obstetrical cases ending fatally in obscure shock in or shortly after parturition, this condition should be considered and searched for. The warning of Eastman is well taken. The diagnosis is easy if sections of lung are available. A death verified as from this cause cannot conceivably be considered the result of poor obstetrics. The condition should not be overdiagnosed but neither should it be underdiagnosed; it should stand on its proper scientific merits.

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## WITHDRAWAL BLEEDING FOLLOWING HEXESTROL AND PREGNENINOLONE ORALLY

FLOYD E. HARDING, M.D., LOS ANGELES, CALIF.

(From the Department of Endocrinology, Ross-Loos Medical Group)

IT IS a well-known fact that after the administration of estrogens in sufficient quantity to a patient with a normal uterus, withdrawal bleeding will occur. Several injections of hormone are used for this purpose. However, Zondek<sup>1, 2</sup> has shown that a strong injection containing estradiol benzoate (2.5 mg.) and progesterone (12.5 mg.), repeated in 48 hours, will usually cause uterine bleeding in a few days. Other investigators have noted that stilbestrol given orally can be used for the same purpose.

The oral use of stilbestrol produces satisfactory withdrawal bleeding, but a large percentage of the patients are nauseated when enough of this substance is given to cause a good flow of blood at a predictable time of onset. Hexestrol causes less nausea than stilbestrol,<sup>3-5</sup> but it is unlikely to produce uterine bleeding in the 1 mg. to 3 mg. daily doses commonly used for therapy of climacteric symptoms.

Because a more satisfactory type of oral therapy was sought, a woman with amenorrhea was given twenty-day courses of hexestrol using larger daily doses during each course. In this manner it was determined that 27 mg. or more daily always caused a light flow of blood lasting four or five days. It was decided to give this treatment to a series of patients to work out the details of a satisfactory method of administration, to determine the percentage of nausea, and to note what beneficial effects were produced. Later pregnenolone was added because hexestrol caused proliferation of the endometrium but no progestational changes.

Obviously, with this treatment there is relief of any estrogen deficiency symptoms and some help to the patient psychologically. Are there any organic benefits? A partial answer to this question is given in the discussion.

In the past, estrogen or pregnenolone has been given to many patients for various purposes.<sup>6-12</sup> Hexestrol has frequently been given for climacteric symptoms.<sup>13-23</sup> Cinberg has used stilbestrol and pregnenolone orally in the treatment of functional amenorrhea.<sup>24</sup>

### Method of Administration

Hexestrol\* was administered in 3 mg. tablets in three or four doses daily. The total amount given daily ranged from 9 mg. to 48 mg. Each original course of treatment lasted twenty days. On succeeding months the medication was usually taken from the fourth to the twenty-fourth days of the cycle so that bleeding occurred about every twenty-eight days. If it occurred

\*The hexestrol tablets were obtained from The Wm. S. Merrell Company of Cincinnati, Ohio.



earlier, the tablets were taken for a day or two longer and vice versa. It was thus possible to create approximately a twenty-eight-day cycle. After two or three periods of artificially produced bleeding, treatment was suspended for a month to see if menstruation would occur naturally. Future therapy was usually given in groups of two courses. When pregnenolone\* was added, it was taken from the eighteenth day of the cycle until bleeding occurred. The 5 mg. size tablets were used in a total daily dose of 5 mg. to 15 mg.

The stilbestrol was given in 5 mg. doses daily for twenty days. When pregnenolone was administered alone, the tablets were given until bleeding occurred or for one month. If menstruation started, the pregnenolone treatment was discontinued for eighteen days and then resumed.

### Clinical Material

There were three cases of primary amenorrhea, fifteen cases of secondary amenorrhea with no bleeding in six months or longer, and ten cases in which the patient menstruated less than six months previously. A physical examination was made, but no evidence of tumor or disease was found. There were thirteen single girls and fifteen married women. Two of the latter had had bilateral oophorectomies. The condition was considered to be functional in the others. Fourteen of the patients had had vaginal smear tests, and all of the slides showed a lack of cornification and a low glycogen content in the cells, indicative of estrogen deficiency. The urinary gonadotropins ranged from 6 M.U. to 42 M.U. per 24 hours in the nine patients tested, consistent with estrogen deficiency. The urinary estrogens were as low as 3 M.U. and as high as 39 M.U., averaging 18 M.U. per 24 hours in seven women. Sterility was a problem in eight women who wanted to become pregnant.

### Results With Hexestrol

Twenty-five patients, or 89 per cent of those treated, bled after hexestrol withdrawal. In three of these patients bleeding started after the second course of therapy but not after the first. Three patients did not bleed, but they had been given only one course of treatment. Two of these bled following twenty days' administration of stilbestrol, 5 mg. daily, and the third had a light flow after adding pregnenolone to the hexestrol in the second course of treatment. Twenty patients bled lightly and five moderately. The flow began on an average of four days after withdrawal of the estrogen and lasted an average of four days. There was no complaint of pain during the bleeding. Only seven women had a spontaneous menstrual period about a month following the withdrawal bleeding. Four patients previously considered to be sterile became pregnant immediately after treatment or a short time later.

There were several other physical changes due to hexestrol administration. Vaginal-cell cornification improved, and the vaginal moisture increased because of greater mucus secretion from the glands. Some improvement occurred in the uterus and accessory genitals when these parts were underdeveloped. There was greater fullness and increased sensitivity in the breasts.

All symptoms of estrogen deficiency such as nervousness, mental depression, dizziness, headaches, palpitation, hot flushes, etc., stopped during hexestrol medication.

\*The pregnenolone (Pranone) was obtained from the Schering Corporation, Bloomfield, N. J.

There was a distinct psychological advantage from the production of bleeding, and several patients stated that they felt more like they had before the onset of the amenorrhea. The administration of psychotherapy was facilitated. The four women who became pregnant were highly pleased with the result.

#### Results With Other Methods

Four patients of eighteen treated with pregnenolone alone bled more regularly. Twenty of twenty-one patients given hexestrol and pregnenolone had withdrawal bleeding. The amount of flow was slightly greater in some women after pregnenolone was added. Six of seven patients who were able to take stilbestrol 5 mg. daily for twenty days had uterine bleeding.

#### Toxicity

Three patients, or 10 per cent of those treated, developed nausea of a mild nature. One of these women complained of dizziness. No other bad effects were observed. This record was very good compared to nine patients given 5 mg. of stilbestrol daily. Treatment had to be discontinued in six of them, or 66 per cent, because of nausea. However, even though nauseated, four of the six took the tablets for the first twenty-day course. Nausea also developed in a high percentage of nonpregnant women who were taking 5 mg. of stilbestrol daily for various conditions other than amenorrhea.

#### Discussion

Hexestrol was found to be satisfactory for the production of estrogen withdrawal bleeding. Its use was preferred to that of stilbestrol because it could usually be given without nausea.

It was possible to predict the approximate date of the onset of bleeding and to cause a cyclic flow about once a month. The amount of blood was less than that of a normal menstruation, but the addition of pregnenolone caused a slight increase in this respect.

The cost of producing uterine bleeding was small when hexestrol was used, and it was much greater when the necessary amounts of the natural estrogens were given. However, some of the natural estrogens had an advantage in an occasional case in that they could be given without the production of nausea.

Symptomatic and psychic improvement was gratifying and, although the patients were told that the benefit was likely to be temporary, this seemed to make little difference. They regained confidence knowing that a treatment was available. The psychological advantages should not be minimized or overlooked. An opportunity would have been missed if available time during the treatment period was not used to convince the patient that she would remain in good health, even though menstruation did not occur in the months following treatment.

Of eight women who were trying to become pregnant, four succeeded. Although this therapy is not recommended for the routine treatment of sterility, it might be tried with benefit after conventional methods have failed.

There was development of the uterus in some of the patients in whom this organ was small and when menstruation occurred spontaneously in the following months, improvement seemed to be permanent.

Theoretically, patients with primary ovarian failure and a normal pituitary have an excessive secretion of pituitary gonadotropin. The ovary is under continuous stimulation. The physiologic, monthly, cyclic formation of gonadotropin no longer exists. However, the administration of hexestrol in large doses for twenty of each twenty-eight days inhibits function of the ovary and pituitary and stops gonadotropin production. During the eight days when no medication is being given, the ovary is again stimulated by the pituitary, possibly improving ovarian function in some women.

### Summary

It was possible to produce withdrawal bleeding from the uterus at regular predictable intervals by the administration of hexestrol. This method of treatment was found to be safe and economical. There was a low incidence of nausea. Physical and physiological advantages were largely temporary but of definite aid for specific purposes. Psychological benefit was frequently obtained.

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## A VERSATILE SELF-RETAINING TRIGGER CANNULA AND TRACTION TENACULUM FOR MODERN TUBAL INSUFFLATION AND UTEROSALPINGOGRAPHY

EDWARD KAHN, M.D., NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, Sydenham Hospital)*

MODERN technique, with accurate recording devices for tubal insufflation and uterosalpingography,\* requires a uterine cannula providing not only a gas-tight seal of the cervix for a leakproof connection between the apparatus and the pelvic cavity, but versatility to meet every contingency.

The trigger cannula (Fig. 1, a) is admirably adapted to cope with the many variations in size, shape, patency, anomalies, tumefaction, version, flexion (or combinations), met in private and clinic practice.

Newly effective occluding power is available, aided by the elasticity, resilience, and moulding quality of the rubber acorn obturator (J).

A normal external os is not necessary to obtain a leakproof seal. A portion of the acorn enters the cervical canal and occludes by direct pressure against the walls.† The smoothness of the procedure minimizes discomfort and trauma. Little time is required. The position of the uterus is not disturbed by cannulization.‡

The uterus is not displaced by the upward push of the cannula, or the downward pull of the tenaculum, because the "pull" and "push" are synchronized by the new trigger-squeezing maneuver which balances the two opposing forces, and applies them simultaneously with one hand. There is no longer any need for the operator to struggle with the cannula and tenaculum, to engage and hold them in a self-retaining manner.

The cannula gives peak performance when used with the new stainless steel traction tenaculum (D).§ However, it is able to accommodate any tenaculum or vulsellum made, from the longest to the shortest, regardless of the shape or type. It does this readily at any point of the cervix with complete ease.

The stainless steel tenaculum has new features. The design of its angular jaw, and its two finely tapered  $\frac{1}{4}$  inch teeth (O), which engage the cervix at a lower level than the shaft, but at right angles to it, give it the efficiency as a traction device which earned it its name.|| Its design, including the gracefully curved shaft, gives greatly improved access to the cervical canal without distortion. Surprisingly little trauma or bleeding results from application or removal.¶

The  $8\frac{1}{2}$ -inch length is an advantage over shorter or longer instruments, and permits the removal of a plastic bivalve speculum of the Graves type (R), and its reinsertion, without disturbing either the cannula or tenaculum. This speculum# is also transparent to x-ray, of utmost convenience in uterosalpingography.

\*Testing of the cannula was done with the Kidde Tubal Insufflator, manufactured by the Kidde Manufacturing Co., Bloomfield, N. J.

†A larger acorn is used for the oversized patulous cervix. Acorns are readily interchanged.

‡Cannulization, a new term denoting the insertion of a uterine cannula with obturation of the cervix in a self-retaining manner.

§The cannula and tenaculum presented here are made and distributed by Clay-Adams Co., 141 East 25 St., New York, N. Y.

||A tenaculum is ordinarily a device to hold with but not for pulling or traction.

¶Removed by deliberate opening and withdrawal.

#NEICO plastic bivalve speculum, manufactured by the National Electric Instrument Manufacturing Co., Elmhurst, L.I., N. Y.



The speculum may be closed as pictures are taken, or withdrawn if technique calls for turning the patient.

The length of the cannula tip (K) is readily adjusted. The position of the acorn is maintained by the acorn collar screw (I). The tip is very malleable and may be rotated by turning the cannula shaft. Adjustments are, thereby, readily made for unusual depth, flexion, version, or any other distortion due to stenosis, spasm, or tumor. Occasionally, a fine two-blade uterine dilator is used before the cannula is introduced. The cannula tip has the narrowest practical diameter and is highly polished. Its end is open with four other openings near it. The tip may be passed to any point in the uterine canal.

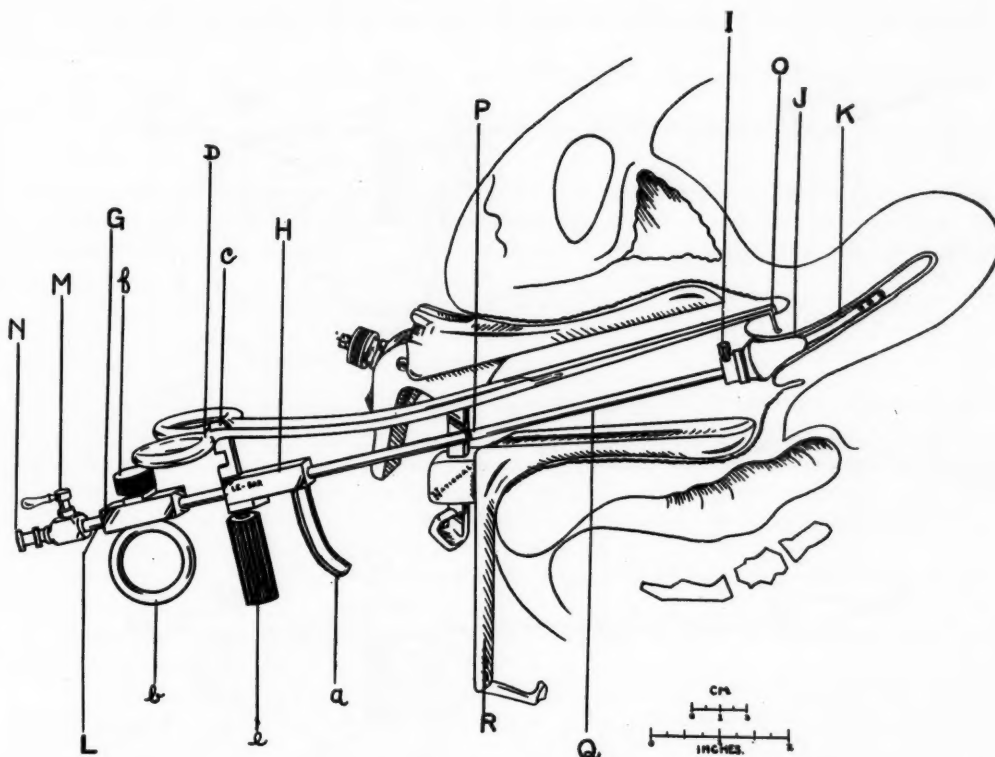


Fig 1.—Diagram showing the trigger cannula and traction tenaculum obturating the cervix with a standard rubber acorn. The tip of the uterine shaft is in the uterine canal.

H, tenaculum control: a, trigger, c, wing, e, set screw; G, cannula control: b, thumb ring, f, set screw; L, stainless steel control shaft; q, uterine shaft; P, junction of L and Q; K, malleable rotatable tip of uterine shaft; M, valve; N, luer connection; J, rubber acorn obturator; I, acorn collar and set screw; D, tenaculum cross bar; O, tenaculum jaw; R, speculum.

Provision is made for the development of deftness in inserting the cannula, and manipulating the controls. After insertion, the forefinger is placed behind the trigger to allow movement up and down the shaft (Fig. 3), with control screw open; after tenaculum is engaged, trigger is squeezed by both fingers again (Fig. 2).

A fine sense of balance is obtained by holding the instrument with thumb through thumb ring (b), and the fore and middle fingers about the trigger (a), set at the middle of the stainless steel control shaft (L). Because of this feature the cannula is a good uterine sound.

A safety feature is provided by the tenaculum control screw (e). A slight turn is all that is necessary instantaneously to break the cervical seal, with release of gas or oil pressure, if the slightest distress is shown by the patient.

Conversely, the seal is quickly tightened by "taking up the slack" with the trigger technique. Occasionally, during an uneventful procedure at higher pressures, a slight leak is noted. This is also readily dealt with.<sup>5</sup> The question arises as to whether the tone and bore of the cervix change due to the counter pressure of all obturators. The tenaculum technique provides a means of coping with this phenomenon when it occurs.

The tenaculum control screw is new in design. It is hollowed out for lightness and rapid cooling after sterilization. Its generous proportions provide excellent control and provide a plumb-bob action, returning the tenaculum control wing to the upright position automatically. A half turn holds it in any position it is turned to without further adjustment. A full turn secures it. The stainless steel shaft is very hard, and is not cut or nicked by the set screw.

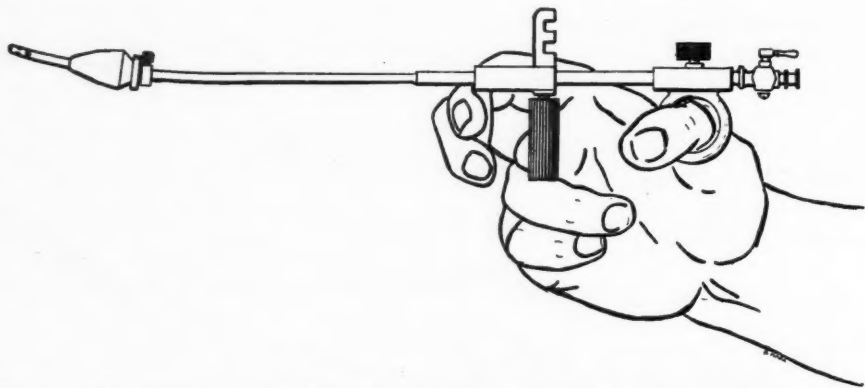


Fig. 2.—The proper way of holding the cannula for insertion into the uterus. The thumb is through the thumb ring and the fore and middle fingers are about the trigger set on the shaft.

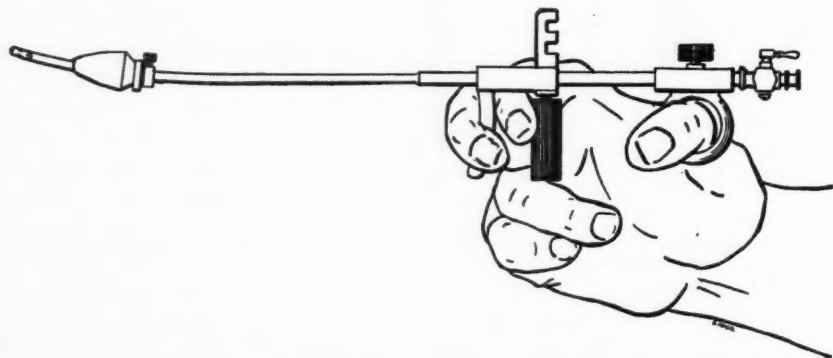


Fig. 3.—The way the tenaculum control is moved up and down the shaft to engage the tenaculum. The middle finger remains around the trigger while the forefinger is placed behind it. The tenaculum control set screw is loose.

The thumb ring, also, has a plumb-bob action when its set screw (f) is released. The thumb-ring cannula control is turned to wherever the trigger is. This, in turn, is determined by the position of the tenaculum on the cervix. The two controls act well together regardless of their position on the circumference of the control shaft.

The cannula control ring (b), when turned to the horizontal position, serves the original purpose of the cannula rings, two in number, namely, to hold the cannula when using a syringe.<sup>1</sup> It also provides for a shorter finger span to the trigger, and, when pre-set approximately where the tenaculum control will come when the tenaculum is fully engaged, acts as an auxiliary stop to prevent a possible "harpooning" action by the cannula, while it is

being "pushed," should it slip through the rubber acorn. This is a possibility if the acorn collar is not tightened. The acorn screw has a heavy thread and will not fall out.

The tenaculum control wing is nonobtrusive, and performs without obstructing the view of the cervix. It does not interfere with turning the patient. It engages either the cross bar (D) or the ring front of the tenaculum. The upper notch is more convenient when engaging a large cervix, the lower one for smaller cervixes.

The cannula is of standard length, light in weight, compact, heavily chrome-plated, and functional in every way. All parts are durable for long years of hard use. The cannula is easily cleaned. It is sterilized by boiling or autoclaving. It fits readily into the average sterilizer.

An adapter, to connect an oil reservoir or syringe vertically, is available. It connects to the Luer end (N),

The cannula has a shut off valve (M) of utmost convenience during uterosalpingography.

A new cannula stand has been designed to support the cannula between the legs as the patient lies on the x-ray table.

It adjusts to a maximum height of 8 inches. It supports the cannula to prevent drag on the cervix, and permits security for the attachment of an oil reservoir or a syringe. It attaches to the stainless steel shaft in front of the valve (L). It is light, compact, and easily dismantled.

A clip-on light attaches to provide focused light on the cervix.

### Summary

A new, versatile, self-retaining trigger cannula, adapted for use with modern insufflators, is described, which will readily engage any length, shape, or type of tenaculum at any point on the cervix, by a new trigger-squeezing action which combines "pull" on the tenaculum and "push" on the cannula into a synchronized, balanced maneuver with one hand, and does not alter the anatomical position of the uterus, yet provides newly effective, nontraumatizing cervical obturation with a soft rubber acorn.

Other features include a very malleable tip, adjustable as to length, which may also be rotated.

Deftness in introducing the cannula is soon acquired because of the trigger grip and multipurpose thumb ring.

The plumb-bob action of the controls is pointed out, as is the safety feature of the tenaculum control screw which quickly releases gas or oil pressure from the cervix by a half turn.

A cannula stand to support the cannula during uterosalpingography, and to provide light to the cervix is described.

A right-angled adapter to hold a syringe vertically is described.

A traction tenaculum is discussed, including its design for pull on the cervix, greater access to the cervical canal, and the way it permits removal and reinsertion of a plastic x-ray-transparent bivalve speculum with open side.

The advantages of the tenaculum method are pointed out.

Reference is made to changes in the tone and bore of the cervix during cannulization, and how leaks thus arising are readily controlled by the tenaculum.

I wish to express grateful acknowledgment to Dr. Julius Jarcho and Dr. Peter Murray of the Department of Obstetrics and Gynecology of Sydenham Hospital for their kind cooperation in the experimental phases of the trigger cannula and traction tenaculum.

I also express my gratitude to Dr. George Berson and Dr. Leon Zussman of the Department of Obstetrics and Gynecology of Sydenham Hospital.

I also wish to express my thanks to Faith Hope Kahn, R.N., for her assistance during the research and clinical testing of the instrument and also her patience in the preparation of this manuscript.

### Addendum

For special work, the trigger cannula is now available with interchangeable uterine shafts at junction (P) of control shaft (L) and uterine shaft (Q). The uterine shaft connects at (P) by a Luer connection. Thus, narrower bore is available when indicated, as in the occasional severe cervical stenosis, or for use with an inflatable obturator. The trigger technique and traction tenaculum are used as with the acorn obturator for introduction and to apply sufficient traction on the cervix to prevent the inflated obturator from ballooning out of the cervix, especially when it is slightly patulous.

The use of special obturators, acorn and inflatable, and uterine shafts (tips) including biopsy curettes, with the trigger cannula and traction tenaculum, will be the basis of a future publication.

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1 WEST 81ST STREET



## NEW TUBAL INSUFFLATOR WITH AUTOMATIC VOLUME AND PRESSURE CONTROL

OSCAR GLASSMAN, M.D., AND ISABEL BECK, M.D., NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)*

UP TO 1946, the tubal insufflation apparatus in current use required skilled manipulation and constant attention. Carelessness in its use could end in unhappy results.

A few years ago, it occurred to one of us (I. B.) that if the apparatus were simplified and made completely automatic and thereby safe, this would popularize it among physicians and give it a wider range of usefulness in the study of the sterile couple. Accordingly, the problem was taken to Charles Davies, A.S.M.E., industrial designer, who designed and engineered the apparatus herein described. This paper deals with an apparatus which eliminates many of the drawbacks and hazards of the current insufflation machines, and which has been designed in such a fashion that accidents due to failure to take mechanical precautions are impossible.

The principle embodied in the final production model herewith illustrated is that of a constant pressure-maximum volume gasometer. By the use of this device, the total uterine pressure is automatically controlled so that at no time can it exceed a pressure of 200 mm. mercury. Moreover, at no time during a test can more than 100 c.c. of carbon dioxide be injected into the uterus.

The machine has been designed for utmost simplicity. On the front panel are two dials. The large central one is the electrically operated kymograph with a special chart designed for clear visibility. The lower right hand dial B indicates the volume of gas in the storage chamber. Beneath this dial is a push button C, which charges the gasometer. In the center of the lower panel is the electric switch D, which operates the kymograph. On the left-hand side is a knob F, marked 0, 30, and 60, which controls the speed per minute in cubic centimeters of the gas flow. Beneath this knob is the outlet E, into which the cannula is plugged.

The push button C actuates a two-way bypass valve. This device contains two valves, one leading to the gasometer, the other to the cannula outlet. It operates as follows: When the button is pressed, it opens the connection between the gas storage chamber and the gasometer, and at the same time closes the connection to the cannula. Gas then fills the gasometer. When the button is released, it closes the connection between the gas storage chamber and the gasometer and opens the one leading from the gasometer to the cannula. Thus, it is possible to recharge the gasometer, if it becomes necessary, without removing the cannula from the cervix.

The rate of gas flow through the cannula is controlled by a needle valve, which is operated by the knob F. This can be set at any speed up to 60 c.c. per minute.

The whole machine is enclosed in a sturdy portable aluminum cabinet and weighs twenty-five pounds. Provision is made to store one dozen cartridges, the cannula and the writing ink under the lid of the cabinet.

*Operation of the Apparatus.*—To charge the apparatus, a carbon dioxide cartridge is screwed into the opening at A. The needle on the lower right hand dial B, which indicates the quantity of gas in the storage chamber, will swing over to "full." By pushing the button C, gas enters the gasometer and forces the piston G to rise. This piston is calibrated so that when it reaches the mark, zero, the gasometer contains 100 c.c. at a pressure of 200

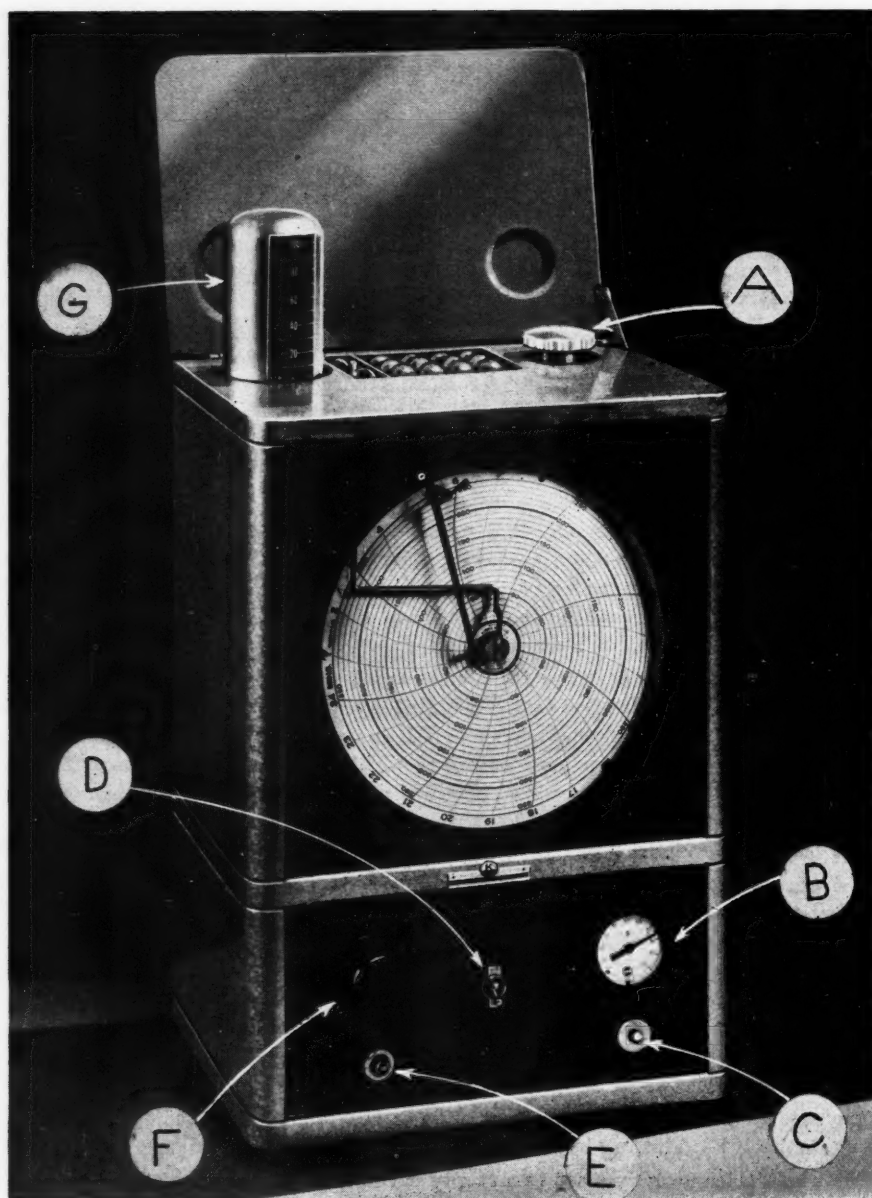


Fig. 1.—Tubal insufflator.

mm. mercury. Even if the push button is held down after the piston has attained its maximum point, the pressure and volume will not exceed the limits established because of the mediation of a safety valve which allows excess gas to escape.

The apparatus is now ready for operation. The patency of the cannula is tested by turning the knob F to the mark 60, and watching the kymograph needle. If the pressure rises, the cannula is plugged; if it remains at zero, patency is established.

The cannula is introduced into the cervix; the knob F is turned to 60 (rate of flow); the electric switch D is turned on to start the kymograph, and the test proceeds. With a self-retaining cannula, the physician's hands and attention are completely free. Should the pressure reach 200 mm. mercury, there is assurance that it can go no higher so that all danger from this source is eliminated. If, however, the tubes are patent, there is assurance that no more than 100 c.c. of carbon dioxide can possibly be introduced.

In the event that gas has been lost through leakage at the cervix and it is desired to repeat the test, the gasometer can be recharged without removing the cannula or closing the needle valve F. The two-way bypass valve previously mentioned, which is operated by the push button C, prevents gas from flowing through the cannula while the gasometer is being charged. As soon as the button is released, gas will again flow through the cannula.

The kymograph chart is designed for visibility. It has thick rulings at 50, 100, 150, and 200 mm. pressure points, as well as radial markings which indicate three-minute periods. Once tubal patency has been demonstrated and a protracted record of tubal excursions is desired, the knob F can be turned to a point between 30 and 60 so as to slow down the speed at which carbon dioxide enters the uterus. In this way, the amount of gas introduced can be kept at a minimum, assuring the least amount of discomfort to the patient from shoulder pain.

The working model of this apparatus has been in use for over one year by the authors in private practice. A production model is now being used in the Sterility Clinic of the New York Hospital. The apparatus has proved itself to be completely reliable and simple to operate. It eliminates the confusion caused by the numerous controls and the vigilance required in the use of other existing types of apparatus.

(Produced by the Kidde Manufacturing Company, Bloomfield, New Jersey.)

## SUGGESTION FOR IMPROVEMENT OF STIRRUP ATTACHMENT FOR OPERATING TABLES

WILLIAM R. WADDELL, M.D., BOSTON, MASS.

*(From the Vincent Memorial Hospital, the Gynecologic Service of the Massachusetts General Hospital)*

DURING the past year a modification of the usual operating table stirrup attachments for supporting the legs of a patient in lithotomy position has been in use at the Massachusetts General Hospital. Modification of the leg holders which have been standard equipment on operating tables for many years was suggested by the frequent occurrence of calf tenderness and pain following their use. As illustrated below (Fig. 1) the passage of the legs lateral to the vertical supporting rods subjects the calves to considerable pressure. This is not infrequently increased by assistants leaning against the legs. In addition to the discomfort caused the patient it is impossible to distinguish these signs and symptoms from those of early phlebothrombosis and thrombophlebitis originating in the calves. Indeed, pressure and contusion of the calves produced by the old leg holders have frequently been suspected as etiological factors.

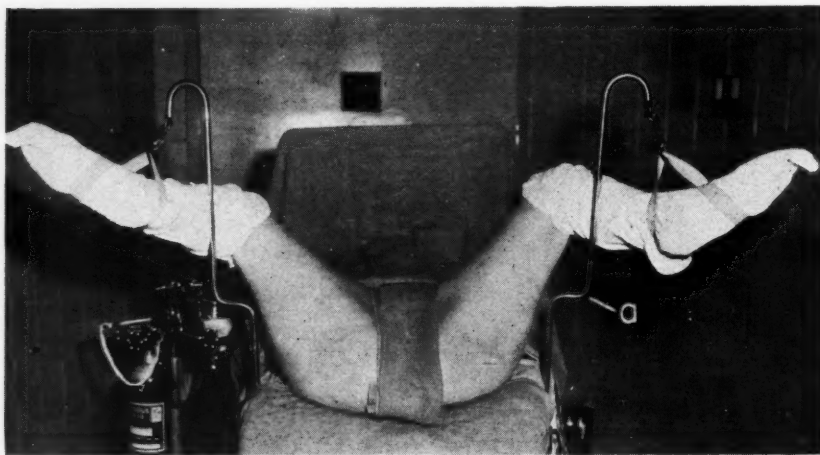


Fig. 1.—The old type leg holders and their method of use. The pressure on the calves is shown. The abduction of the thighs necessary for passage of the legs lateral to the vertical bars subjects the abductor muscles to considerable strain and the tension upon these muscles can be seen.

These considerations have led to the abandonment of mechanical leg holders in some clinics or the substitution of other types of holders which have similar objectionable features or have not given satisfactory exposure of the perineal region.

The shape and method of use of the old and modified stirrups are shown in Figs. 1 and 2. The alterations consist in cutting the bar at "a", reversing the direction of the vertical rod and hook, inserting a 7-inch horizontal extension, and welding the pieces together.



This allows the vertical bar to pass lateral to the legs and still support the legs from the same position as previously. There is no appreciable torque tending to rotate the vertical support since the weight of the legs is supported in a vertical direction and the horizontal thrust falls in the plane of the attachment to the table.

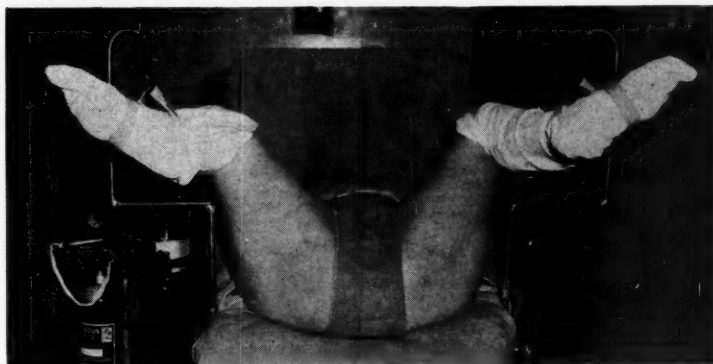


Fig. 2.—The modified leg holders and their method of use. The calves do not touch the supports. The thighs are somewhat more flexed but not abducted unnecessarily. Exposure of the perineal region is fully as adequate as with the other type of holders.

Exposure of the perineal region is entirely satisfactory. The thighs are somewhat more flexed and marked abduction necessary for passage of the legs lateral to the vertical rods of the old stirrups is avoided. Assistants stand in the same position as previously, either inside or opposite the patient's feet.

Any machine shop can alter the old stirrups or construct new ones at slight cost.

Mr. George T. Frawley of the Machine Shop of the Massachusetts General Hospital kindly fashioned the new leg holder from an old one.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Gynecology

**Bassan, D., and Borches, F.:** Acute Ulcers of the Vulva, *Bol. Soc. de obst. y ginec. de Buenos Aires* 26: 68-73, Sept. 12, 1946.

The author, after reviewing Hunt's and Lipschutz's classifications of vulval ulceration, describes a case of acute vulval ulcer in a woman 47 years of age. While she was relieved rapidly with topical sulfonamide powder and 400,000 Oxford Units of penicillin, the author stresses the importance of vitamin B complex deficiencies in these cases, noting particularly moderate ariboflavinosis.

CLAIR E. FOLSOME.

**Borjas, A., and Rodriguez-Diaz, L. H.:** Vesicovaginal Fistula of Tubercular Origin, *Rev. obst. y ginec.* 7: 215-221, 1947.

The authors describe in detail a case of urinary tuberculosis in a girl of 14 years which resulted in the development of an incurable vesicovaginal fistula. Treatment consisted of left nephrectomy and a right ureterocolostomy.

CLAIR E. FOLSOME.

**Bettinger, H. F., and Jacobs, Hubert:** Mesonephroma Ovarii, *M. J. Australia* 1: 100, Jan. 24, 1948.

The authors report a case of this "rare" type of ovarian tumor and review the clinical and pathological findings. The tumor has no endocrine secretions and does not therefore cause any general symptoms that might lead to a specific diagnosis. It is felt that these tumors as a whole should be considered as malignant. A discussion of Schiller's contentions as to the histogenesis of these tumors is presented. The authors urge close observation for further cases of this type of tumor in order to scrutinize a more composite group of such tumors.

WM. BERMAN.

**Fluhmann, C. F.:** The Clinical Significance of Chronic Parametritis, *California & West. Med.* 68: 159, March, 1948.

It has long been recognized that the parametrium plays an important role in serious and extensive diseases of the uterus such as inflammations, carcinoma, and endometriosis. However, the purpose of this report is a study of 54 patients observed in private practice, in whom a variation of symptoms, from vague lower abdominal pain, backache, and leg pains, had been attributed to demonstrable thickening of the sacrouterine ligaments.

A positive diagnosis is based on two procedures which put the cervix on a stretch and thus the inflamed uterosacral ligaments can be definitely felt as tender cords.

The treatment consists essentially of two procedures: In the first place, elimination of any inflammatory lesion of the cervix with or without erosion of that organ; second, the application of heat, which may be accomplished by diathermy or hot Sitz baths with continuous douche. This should be done for twenty minutes once or twice daily.

The results are tabulated. It is noted that, of the 33 patients, 14 were completely free of symptoms and in them no evidence of thickened sacrouterine ligaments could be palpated. Definite improvement occurred in thirteen instances; in six cases there was no relief. However, of those cured or improved, six later returned with recurrence both of symptoms and the physical findings.

JAMES P. MARR.

**Bayan, Flora B.: Increased Incidence of Prolapse of the Uterus as Probable Effect of War,** *Philippine J. Surg.* 2: 201, Sept.-Oct., 1947.

The author reports 32 cases of uterine prolapse admitted to the Philippine General Hospital in nine months, a tenfold increase in incidence as compared with prewar years. This increase is attributed to heavy physical burdens placed on women during the war, and to near-starvation. In 12.5 per cent of these women there were definite manifestations of malnutrition.

IRVING L. FRANK.

### Gynecologic Operations

**Jacobson, Philip: Preservation of Function in Cystic and Sclerotic Ovaries,** *Surg., Gynec. & Obst.*, page 31, July, 1948.

The author presents sixteen patients from whom both tubes and one ovary had previously been removed. These patients were suffering from ovarian insufficiency of the one remaining ovary. Exploration revealed that these ovaries contained numerous small "morbid follicles" which were located just between the white lines and impinged on the vessels and nerves as they entered the ovary. Removal of these follicles with preservation of the ovary brought relief from discomfort and restoration of normal cyclic activity at least temporarily to the patients so treated. The author presents in detail the technique of exploring the hilum of the ovary. A plea is made for more conservative surgery in dealing with this type of case.

L. M. HELLMAN.

**D'Ingianni, Vincente: Reconstructive Surgery of the Fallopian Tubes Employing a Canula,** *South. M. J.* 41: 575, July, 1948.

Surgical reconstruction of occluded Fallopian tubes has been in the past a most unsatisfactory procedure. A review of 818 plastic operations on the tubes resulted in only 36 live-born babies. The new technique here described gave a 20 per cent live birth incidence, as compared with the 6.6 per cent in the large series of 818 operations performed by various techniques and many operators. The technique of this new operation is well illustrated. The tube is divided distal to the occluded portion and a steel cannula 3 cm. long is passed into the liberated, patent lumen. To this cannula there is welded a long flexible wire. An incision is made in the fundus and the tube and its included cannula are passed into the uterine cavity, the wire being forced down through the cervical canal to permit removal of the cannula three months after operation. The serosa of the tube is sutured to the serosa of the uterine fundus. When occlusion at the fimbria is found, the distal portion of the tube must be resected and the serosa and mucosa approximated before transplantation of the proximal cut end of the tube.

WILLIAM BICKERS.

**Bianco, Alfonso A.: Giant Myxoma of the Vulva,** *An. brasil. de gynec.* 24: 345-350, Nov., 1947.

Bianco describes an unusual vulval tumor removed from a 20-year-old patient. The tumor began as a small lesion upon the right labium majus. In four months it had grown so rapidly the patient was unable to walk. The mass was removed under local anesthesia. It weighed 6 kg. (13¼ pounds) and measured 42.0 by 29.0 cm. (about 17 by 11 inches). It was multilobulated with 9 major lobules. Microscopic study revealed it to be a myxoma. Three photographs and a good bibliography of these rare lesions are included in the article.

CLAIR E. FOLSOME.

**San Martin, H. G.: An Illustration of Conservative Gynecologic Surgery, Obst. y ginec. latino-am. 5: 496-500, Oct., 1947.**

The author, Professor of Clinical Obstetrics at Uruguay National Medical School, Montevideo, emphasizes his plea for conservative gynecological surgery by presentation of a unique case report. A 20-year-old primiparous patient, after several outside attempts to produce an abortion, from a three months' pregnancy, with some caustic intrauterine substance, was operated upon from above and a partial hysterectomy was performed. The fetus was dead. Four months later the patient became pregnant again, despite advice to the contrary, and was delivered ultimately of a living child weighing 4,100 Gm. Her recovery was full and complete.

CLAIR E. FOLSOME.

### Labor, Management, Complications

**Perez, Luis, and Blanchard, Oscar: Prophylactic Local Chemotherapy in Operative Obstetrics, Anales del Instituto de Maternidad y Asistencia Social, "Professor U. Fernandez" 7: 9-26, 1945.**

The authors reporting from the de Alvear Hospital of Buenos Aires, review their experiences following the use of 5.0 Gm. of sulfonamides which had been placed in the uterine cavity following operative childbirth; e.g., forceps, and removal of the placenta. The authors have developed an intrauterine instillator, capable of being sterilized, which aids in placement of the sulfonamide powder. In an earlier report they obtained only 5.0 per cent morbidity among a series of 80 cases. To this number 65 more cases are added for a total of 145 cases. They have used the intrauterine application of sulfonamides in more serious indications in the latter series. They obtained an over-all morbidity of 11.8 per cent, most of which were of a mild or transient character.

They conclude that the intrauterine application of sulfonamide powders represents an advance in prognostic progress since the patients obtain prophylaxis against septic complications in operative obstetric deliveries.

CLAIR E. FOLSOME.

**Gillman, J., Gilbert, C., and Gillman, T.: Puerperal Inversion of the Uterus of Nutritional Origin—An Experimental Study in the Albino Rat, South African J. M. Sc. 12: 161, Dec., 1947.**

Five of twenty parturient rats, raised on corn and soybean meal, underwent a spontaneous uterine inversion. These animals were malnourished and stunted, and mild rachitic changes were present in two cases. These observations indicate that mismanagement of the third stage of labor is not the only cause for inversion, but that a metabolic defect may predispose by an impairment of uterine contraction mechanisms.

IRVING L. FRANK.

### Menopause

**Kernodle, John R., and Cuyler, W. Kenneth: Vaginal Cytology of Postmenopausal Women, South. M. J. 41: 861, Oct., 1948.**

Using the technique of Papanicolaou and Traut, the authors have studied and classified the postmenopausal vaginal cytology. They divide the nonmalignant epithelial cells into five types: follicular, regressive, premenstrual, crowded menopause, and atrophic menopause. For still greater definition they employ four additional subtypes which in their opinion clarify the description of cellular morphology. From the study it is felt that the subtypes may represent physiologic, morphologic changes in the vaginal epithelium from the menopause to senility.



Smears suspicious of carcinoma, but not definitely diagnostic were seen most frequently in the regressive type of smear. And the same type was most frequently associated with proved malignancy. Three known malignancies were not diagnosed by either vaginal or cervical smears, an error of 4.2 per cent. There were 70 cases of proved malignancy and, of these, 12.9 per cent were diagnosed only by cervical smear.

WILLIAM BICKERS.

**Ferguson, Homer E.: The Use of Vitamin E in Menopausal Syndrome, Virginia M. Monthly, page 447, Sept., 1948.**

Indiscriminate use of the estrogens in the treatment of the menopause is fraught with great danger to the patient if used by inexperienced physicians. Sedation and verbal assurance have an important place in the treatment, but the patient demands more. The author seems to think that vitamin E has proved of unquestionable value in certain reproductive disorders of male and female; namely, threatened and habitual abortion and also in certain neuromuscular diseases such as disseminated sclerosis. There are many who disagree. Vitamin E was first used in the menopausal syndrome by Christy and subsequently confirmed by Hain. The author reports experience with some 66 cases using 10 mg. of alpha-tocopherol three times daily for 6 weeks and then 5 mg. daily for indefinite periods. A fair number of these patients received complete relief or significant reduction of symptoms referable to vasomotor instability.

WILLIAM BICKERS.

### Miscellaneous

**Chesley, Ray F.: Progress Report on Observations of the In Vitro Effect on Antibiotics, Sulfonamide Drugs and Combinations Thereof Upon Several Strains of Pathogenic Bacteria, Bull. Margaret Hague Maternity Hosp., page 59, June, 1948.**

The author concludes from in vitro experiments with various chemotherapeutic and antibiotic substances that a combination of penicillin with sulfathiazole is most efficient because it has the widest bacteriocidal range with the lowest cost. He warns against prophylactic use of these agents in dosage or duration that fall short of the full therapeutic range because of the development of increased bacterial resistance. This report emphasizes that these results might differ in vivo, and, therefore, concludes that clinical evaluation would be necessary to supplement these studies.

S. B. GUSBERG.

**Croxatto, H., Croxatto, R., and Reyes, M.: The Effect of Hypertension on the Inactivation of Oxytocin by the Serum of Pregnant Women, Science 108: 658, Dec., 1948.**

In a small series of experiments the authors have shown that the enzyme oxytocinase which ordinarily reacts on the substrate oxytocin to reduce its activity will also exert an inhibitory effect on added hypertensin. The latter slowly disappears as the incubation process progresses and hypertensin is destroyed. Parallel experiments were performed showing that hypertensin also inhibits the inactivation of vasopressin. All of these experiments were performed using rat and guinea pig uteri to measure the oxytocinase activity of the blood plasma. They indicate an extremely close relationship between the enzymatic systems that inactivate hypertensin, oxytocin, and vasopressin. The possibility that these cross effects operate also in vivo is now under investigation.

L. M. HELLMAN.

**Lima, Octavio Rodrigues, and Pereira, Oswaldo Gelli: A Biological Pregnancy Test Using the Male Bufo Marinus, An. brasil. de gynec. 24: 245-252, October, 1947.**

The authors, reporting from the Obstetrical Clinic and Pathology Department of the University of Brazil National Medical School, evaluated a new pregnancy test using the male *Bufo marinus*. Ten c.c. of a morning urine specimen are injected into the dorsal lymph sac.

Urine collected from the cloaca of the toad is examined every thirty minutes over a three-hour period. If the test is positive, numerous and characteristic spermatozoa are found in the cloacal fluid. None are found in a negative test. These toads were found to liberate free sperm consistently into the cloacal fluid when injected with 20 U. of chorionic gonadotropin. Spermatozoa could not be obtained following injections of estrone, progesterone, water, or saline. Increasing the concentration of gonadotropin does not hasten the response to the test. Normally, sperm are found in the cloacal fluid of these gray toads only at time of their sexual embraces.

The authors studied fifty clinical human cases where the amenorrheic period exceeded the usual time of the cycle in a range of 5 to 50 days. They found positive results varied in appearing positive in a time range of 30 to 120 minutes. The results checked in a control series of Friedman tests. They utilized the new test to pick up and operate on two ectopic pregnancies. They conclude the test is valuable, much more rapid, and as reliable as the Friedman test. Five photographs are included.

CLAIR E. FOLSOME.

### Placenta

**Baens, A., and Tancinco-Yambao, G.: Report on 80 Cases of Ablatio Placentae, Philippine J. Surg., March, April, 1948.**

In a twelve-year period there were eight cases of ablatio placentae at the Philippine General Hospital, an incidence of 1:985. The apparent etiologic factors were: toxemias, 21; trauma, 3; pulmonary tuberculosis, 3; appendicitis, 1; acute ileocolitis, 1; and rectal carcinoma, 1. In fifty patients the cause was undetermined. In two-thirds of cases there was abdominal pain and a ligeneous uterus, while the remainder had a lax nontender uterus. Ninety-four per cent of patients had slight to moderate vaginal bleeding. Forty-nine of the patients were delivered vaginally, twenty-four spontaneously.

The gross maternal mortality was nineteen, or 23.75 per cent. Seven deaths were due to peritonitis following cesarean section (including three cesarean-hysterectomies). There were nine hemorrhage-shock deaths, five following cesareans (including two cesarean-hysterectomies), three following vaginal delivery, and one undelivered. Two patients delivered extramurally died of postpartum hemorrhage, and one patient died of uremia. The mortality rate in the group delivered by cesarean section was 40 per cent (usually more seriously ill patients), and in the group delivered vaginally was 6 per cent.

IRVING L. FRANK.

### Physiology of Pregnancy

**Davis, Edward M., and Seski, Arthur: Childbearing in the Twilight Reproductive Period, Surg., Gynec. & Obst., page 145, August, 1948.**

A study is made of the obstetrical histories of 11,011 women, 40 years old and older, who were cared for in The Chicago Lying-in Hospital during the years 1927 through 1944. This study confirms the findings of numerous articles on this subject. The infant mortality of this group of women is definitely higher than the hospital rate over the same period, being 9.5 per cent and 3.5 per cent, respectively. There is approximately a three-fold increase in the incidence of hypertensive complications of pregnancy. Placenta previa and premature separation of the placenta were increased materially. Labor was marked by an increase in operative intervention as a result of pregnancy complications. The authors conclude that there are many real hazards associated with pregnancy in older women.

L. M. HELLMAN.

## Correspondence

### Comments on the Antidiuretic Action of Morphine

*To the Editor:*

In an article entitled "Morphine Suppression of Urinary Output in Pregnant and Nonpregnant Women" (AM. J. OBST. & GYNEC. 57: 302, 1949) Kraushaar, O. F., Bradbury, J. T., Wang, Y. K., and Brown, W. E., referring to our previous work,<sup>1</sup> have concluded: "... that the data from dog experiments, indicating that morphine causes a release of antidiuretic hormone from the neurohypophysis, cannot be accepted in explanation of the antidiuretic effect of morphine in normal women." I should like to take exception to this statement, for I feel that their conclusion is hardly justified. A critical examination of their experimental findings reveals no contradiction, but if anything rather a confirmation of our concept of a neurohypophysial mechanism for morphine antidiuresis.

This concept is based on experiments done on female dogs maintained on standard diets. When such animals in postabsorptive state and in water equilibrium are given water, either by stomach (40 c.c. per kilogram of body weight) or by intravenous infusion (25 c.c. per kilogram), they excrete it practically quantitatively within three hours. The water administered by stomach has been shown to be completely absorbed from the gastrointestinal tract in forty minutes. Morphine, when given either forty minutes after the administration of water by stomach or fifteen minutes before the intravenous infusion of water is started, inhibits water diuresis, the excreted amount falling to 13 per cent (1 to 30 per cent) of the water intake. In dogs with diabetes insipidus produced by interruption of the hypothalamico-hypophysial tract (the so-called neurohypophysectomized animals), morphine does not inhibit the diuresis produced by water given either by stomach or by vein. It has been concluded, therefore, that morphine exerts an antidiuretic effect acting on the hypothalamico-hypophysial system and thereby liberating antidiuretic hormone.

Before examining the data of Kraushaar and co-workers I should like to comment on their techniques. In order to study drug action on water diuresis one must devise a uniform method that produces a clear-cut water diuresis in every subject. In their experiments, the amount of fluid infused into their subjects was not constant, and the time of infusion varied between three and six and one-half hours, while the collection period remained constant (eight hours). During the eight-hour period before starting the infusion of 5 per cent glucose, no fluid was given so that at the start of the experiment the patients were not in water balance. Furthermore, a diuresis induced by 5 per cent glucose solution is hardly the same as that produced by water alone. It is not surprising, therefore, that only a few of their patients returned the entire water load within the eight-hour period of observation. These results clearly indicate that the method devised for inducing water diuresis was not suitable.

It is well established that pregnant women have a greatly increased volume of body water and in view of this fact and the other variables involved in water exchange they should not be compared with nonpregnant women with diabetes insipidus. This criticism is justified since the pregnant woman, M. B., showed no significant antidiuresis with 2 units of aqueous Pitressin, while the nonpregnant patient, M. S., showed a significant antidiuretic effect with 5 units of Pitressin tannate in oil. (Comparable controls would, of course, have been more informative.)

In considering the data on the nonpregnant woman one can see a striking difference in morphine action on the normal patients and on the patients with diabetes insipidus. In the normal patients there appears to have been a striking oliguria during the peak of morphine action amounting to an almost complete suppression of urine flow. In the two patients on whom detailed protocols are available, Kraushaar and associates report marked inhibition of water diuresis (5 per cent of the control excretion for E. M. and 8 per cent for E. S. for the eight-hour period). In the first group of nine normal nonpregnant women detailed data are not available, but it appears that the women eight hours after morphine excreted 48 per cent of the amount put out in the control period. It is hard to understand this startling difference in morphine action. In contrast is the finding of a relatively small decrease in the patients with diabetes insipidus (66 and 72 per cent, respectively, of the control excretions). The fact that some decrease in the diuresis occurred may be attributed to some factors altering renal dynamics or more probably to a minimal output of antidiuretic hormone from small neurohypophyseal remnants. These patients cannot be assumed to have maximal polyuria, such as occurs when there is complete absence of antidiuretic-hormone-producing tissue, merely on the basis of the saline infusion test of Hickey and Hare (incorrectly attributed to Carter and Robbins who merely confirmed the original observations).

Although Kraushaar and co-workers do not mention the severity of the diabetes insipidus in their patients, I would infer from their published charts that the patient L. B. excreted about 6 L. of urine per day and the patient M. D. between 3 and 4 L. per day. If these estimates are correct, it would seem certain that these patients were far from having the maximal polyuria which is characteristic of the individual with no antidiuretic-hormone-secreting tissue. It will be recalled that in the total absence of the antidiuretic hormone 12.5 per cent of the glomerular filtrate appears as urine. Thus, if the facultative reabsorption—normally controlled by the antidiuretic hormone—fails to occur, one-eighth of the 180 L. (130 c.c. per minute multiplied by 1,440 minutes per day), i.e., 20 L. of urine are excreted each day. In a hydrated patient with diabetes insipidus smaller output might be ascribed to low rate of glomerular filtration or to the presence of a small amount of antidiuretic hormone secreted from uninvolved neurohypophyseal tissue. In response to morphine stimulation, these remaining cells appear to put out augmented amounts of hormone. This may well be the case in the patients reported by Kraushaar and co-workers. In any case, I feel sure that the marked suppression of diuresis seen in the normal women contrasts so impressively with the slight change in these patients with only incomplete diabetes insipidus that one cannot deny the importance of the neurohypophyseal mechanism in morphine antidiuresis in human beings.

Kraushaar and associates place a great deal of weight on the failure of the patients, pregnant and nonpregnant, to show a chloruresis with morphine. In our dogs we were usually but not always able to demonstrate an increase in total chloride output after morphine. This is in good agreement with the results of the workers using physiologic doses of Pitressin (1 to 15 milliunits).<sup>2,3</sup> Stimulation of neurohypophysis likewise produces an increase in total chloride excretion only part of the time. It seems unnecessary to place so much emphasis on so controversial a change as chloruresis especially when the findings are at best equivocal. The crucial experiment would be the study of the effect of morphine on water diuresis in patients with complete diabetes insipidus.

It seems to me that it is very difficult to draw any conclusions from the data presented by Kraushaar and co-workers. I certainly cannot see any experimental fact in their work that would contradict our concept, namely that the hypothalamico-hypophyseal system is involved in morphine antidiuresis.

RICHARD C. DE BODO

NEW YORK UNIVERSITY COLLEGE OF MEDICINE  
DEPARTMENT OF PHARMACOLOGY  
477 FIRST AVENUE  
NEW YORK  
MAY 28, 1949



### References

1. de Bodo, R. C.: *Pharmacol. & Exper. Therap.* 82: 74, 1944.
2. Shannon, J. A.: *J. Exper. Med.* 76: 387, 1942.
3. Anslow, W. P., Jr., Wesson, L. G., Jr., Bolomey, A. A., and Taylor, J. G.: *Federation Proc.* 7: 3, 1948.

### Reply by Drs. Kraushaar and Bradbury

*To the Editor:*

The impetus and the pattern for our recent observations developed largely from de Bodo's excellent studies. In our study, the dosage of morphine and the quantities of fluid administered were limited to those that are commonly employed in the clinical management of patients. Under these conditions, morphine injections were consistent in suppressing urine volume but did not produce a chloruresis. Our conclusions should be interpreted as indicating that the findings in women failed to give any positive evidence on the mechanism of action of morphine, but in no way do they detract from the validity and decisiveness of de Bodo's contributions.

De Bodo's criticism, that the amount of fluid and the duration of the infusion were not constant in our patients, is valid, but, we think, unimportant. Each woman was regarded as an experimental unit, who could be treated as a control on one day and as an experimental subject a few days later. Such a program is logical as long as the amount of fluid and the rate of injection are kept constant during the two study periods in the same patient. This provides a better comparison than using different individuals for the control and experimental tests.

We are not impressed by his suggestion that our subjects were not in water balance at the beginning of the infusion. Strictly speaking, a person would never be in water balance unless a continuous infusion were being given which would equal the urine flow plus the insensible loss. Furthermore, experiments in our laboratory have shown entirely comparable urine volumes following the administration of equal volumes of fluid, whether it be water by mouth, or 5 per cent or 25 per cent glucose solution given intravenously. (Glucose is grossly overrated as a diuretic agent.) Since these observations were preliminary to an evaluation of the therapeutic use of morphine in women with toxemia of pregnancy, we were primarily interested in determining whether morphine would alter the response of a patient given intravenous fluid to overcome an existing oliguria or anuria. Thus it was not our purpose to study patients who were overhydrated and who would therefore exhibit a maximal diuresis.

His objection to comparing the effects of Pitressin injections on pregnant and non-pregnant women is certainly valid. We attempted only to compare the effect of morphine and Pitressin on the same pregnant woman in whom Pitressin caused a chloruresis and an antidiuresis for the first two hours. The limitations of our observations on the patients with diabetes insipidus were noted in our original communication, "while it is not possible to determine the exact amount of posterior pituitary still functioning in patients with diabetes insipidus, these individuals offer the only means of comparison with stalk-sectioned laboratory animal." The fact that oral fluids, except for those in the diet, were withheld for sixteen hours caused a reduction of the total twenty-four hour output of urine to that noted on the charts. Thus the test days did not reveal the severity of the diabetes insipidus.

The determination of urinary chlorides was included since de Bodo had reported a fifty fold increase in the concentration of chlorides in the urine and a twofold increase in the total excretion of chlorides in spite of the marked decrease in urine output in the first three hours following the injection of morphine in dogs. The lack of a chloruresis in our experimental subjects may be due to a species difference in response, although now de Bodo seems to minimize its significance. That morphine tends to produce an oliguria in normal pregnant and in nonpregnant women is in complete accord with de Bodo's findings in dogs, despite differences in preliminary hydration and marked differences in dosage

of morphine. It is also probable that adequate clinical studies will yield positive evidence to confirm his concept of the hypothalamico-hypophysial system being involved in morphine antidiuresis; our evidence, being negative, is not contradictory.

OTTO F. KRAUSHAAR, M.D.  
JAMES T. BRADBURY, Sc.D.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY  
STATE UNIVERSITY OF IOWA  
IOWA CITY, IOWA  
JUNE 25, 1949

### **Fetal Heart Rate and Posterior Pituitary Extracts by Intravenous Drip**

*To the Editor:*

Rupture of the uterus is recognized as a rare but definite danger associated with the use of Pituitrin intramuscularly for induction of labor. With the increasingly widespread use of this agent by intravenous drip, there appears to be danger to the fetus, but it is a danger which due attention to essential precautions will prevent. In some unpredictable instances, marked and prolonged slowing of the fetal heartbeat may occur. The uterine sign for this is a sustained uterine contraction lasting many minutes and involving the entire uterus or only its upper part. Normal fetal heart rate returns at once, upon decrease in the rate of administration or complete withdrawal of Pituitrin. Relief of fetal distress is associated with prompt relaxation of the uterine contraction and establishment of rhythmic activity. Our experience is as follows:

Records of uterine contractions have been made with a two-channel, ink-writing strain-gage tokodynamometer similar in principle to the three-channel one reported by Reynolds, Heard, Bruns, and Hellman (1947). Activity is recorded from the middle portion of the upper third of the uterus (fundus) and from the middle of the lower third of the uterus (lower uterine segment.) Intravenous drip of Pituitrin (1:5,000-10,000 concentration) is begun by way of the cubital vein.

Pituitrin was administered for the purpose of inducing labor or of accelerating an otherwise prolonged first stage of labor. At the time of injection a team of two was stationed with the patient constantly, one to observe the subject, to listen to the fetal heartbeat, and to regulate most carefully the rate of the intravenous drip; the second member of the team to operate the tokodynamometer and to watch the record of the activity of the uterus.

Upon starting the intravenous drip a period of adjustment was usually required to establish a flow at the desired rate of 0.5 minim per half-hour or less. During the period of fluctuation in the rate of flow the uterus responds promptly, contracting only in the upper region. On two occasions, at the onset of the administration of Pituitrin for induction of labor, sustained contractions lasting for several minutes were observed. In one, the fetal heart rate prior to the injection was 120 per minute. During a contraction lasting seven minutes the fetal heart rate diminished to 88 per minute. In the second case, the fetal heart rate dropped from 168 per minute to 80 per minute during a contraction lasting ten minutes. Upon withdrawal of the Pituitrin the uterus promptly relaxed and the fetal heart rate returned to normal.

In view of the fact that this result was observed in two instances where Pituitrin was used in the dilutions mentioned above, we believe that a warning should be sounded with respect to this danger. Theobald and associates and Hellman and associates have noted this effect, but have not stressed it. Although the published reports on this technique are few (Hellman, 1949; Hellman, Harris and Reynolds, 1949; Stone, 1949; Theobald, Graham, Campbell, Gange, and Driscoll, 1948), reports of its use made to several societies have led to rather widespread adoption of this procedure at the present time in several metropolitan areas in this country. As a result, the technique is now becoming recognized as one of considerable potential value. It offers a means of continuous, even dosage and

ease of withdrawal in the event of adverse effects. The principal effect obtained following intravenous use is that of accentuating a normal physiological gradient of activity from the fundus toward the lowermost part of the uterus (Hellman, Harris and Reynolds, 1949).

The necessary precautions to safeguard against too great a uterine response at the commencement of the intravenous drip include the following steps:

1. An observer should listen frequently to the fetal heart.
2. One operator should adjust the flow critically from zero to the desired frequency per minute. In so far as possible, adjustment of the drip should be made prior to the venous infusion in order to maintain a slow minimal rate of injection.
3. A shut-off valve near the needle should be used.
4. Standardization of needle size, length of tubing, and critical adjustment of the drop control device for complete control with respect to constancy and size of the drop are important.
5. A recorder of uterine contractility should be used to confirm the fact that a spasm of the upper part of the uterus is not elicited. If such a response occurs, the observer is warned and the record gives proof of subsidence of the danger following withdrawal of the Pituitrin.

These observations were made during a study currently in progress at Cumberland Hospital, conducted jointly by the Department of Embryology, Carnegie Institution of Washington, Baltimore, and the Department of Obstetrics and Gynecology, Cumberland Hospital, Brooklyn, N. Y. This work is aided by a grant from the Kate Lubin Research Foundation, Inc. The participants in this study include Samuel R. M. Reynolds, Ph.D., Richard Waltman, M.D., Barnet Delson, M.D., Leslie Tisdall, M.D., and the undersigned.

SAMUEL LUBIN, M.D.

847 PARK PLACE  
BROOKLYN 16, N. Y.

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4. Stone, M.: AM. J. OBST. & GYNEC. In press.
5. Theobald, G. W., Graham, A., Campbell, J., Gange, P. D., and Driscoll, W. J.: British M. J. 2: 123, July 17, 1948.

### Erratum

On page 1039 of the June, 1949, issue of the JOURNAL, in the article on "Nutrition and Human Reproduction: An Historical Review," by Robert D. Mussey, the word "colored," referring to drawings in the *Rosengarten*, 1513 edition, should be omitted.

## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Joseph Baer. *Secretary*, Norman F. Miller, 1313 East Ann St., Ann Arbor, Mich. Next meeting, May 11, 12, 13, 1950, The Greenbrier, White Sulphur Springs, Va.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, Samuel A. Cosgrove, Jersey City, N. J. *Secretary*, L. A. Calkins, University of Kansas Medical Center, Kansas City 3, Kansas. Annual meeting Hot Springs, Va., September, 1950.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, George Kamperman, Detroit, Mich. *Secretary-Treasurer*, John I. Brewer, 24 West Ohio St., Chicago 10, Ill. Annual meeting to be held Thursday, Friday, and Saturday, Sept. 21, 22, and 23, 1950, at the Hotel Schroeder, Milwaukee, Wis.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, C. J. Andrews, Norfolk, Va. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Next meeting, Feb. 9, 10, and 11, 1950, Hotel Roanoke, Roanoke, Va.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1950.
- New York Obstetrical Society.** (1863) *President*, Albert H. Aldridge. *Secretary*, Claude E. Heaton, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Newlin F. Paxson. *Secretary*, George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Eugene A. Edwards. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, Henry S. Acken, Jr. *Secretary*, J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Houston S. Everett. *Secretary-Treasurer*, W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Edward Friedman. *Secretary*, Lester J. Bossert, 2404 Auburn Ave., Cincinnati 19, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Rudy F. Vogt. *Secretary-Treasurer*, Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, R. A. D. Gillis. *Secretary*, Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.
- Obstetrical Society of Boston.** (1861) *President*, M. Fletcher Eades. *Secretary*, H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Philip H. Arnot. *Secretary-Treasurer*, R. Glenn Craig, 490 Post St., San Francisco, Calif.
- Washington Gynecological Society.** (1933) *President*, George Nordlinger. *Secretary*, Stafford W. Hawken, 1150 Connecticut Ave., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Conrad G. Collins. *Secretary*, E. W. Nelson, 1407 S. Carrollton Ave., New Orleans, La. Meetings held October, November, January, March, and May.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.



- St. Louis Gynecological Society.** (1924) *President*, A. N. Arneson. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Donald W. de Carle, 2000 Van Ness Ave., San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Julius McIver, Dallas. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex. Annual meeting, Dallas, Texas, September, 1949.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, O. W. Picard. *Secretary*, Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Gynecologists and Obstetricians.** (1938) *President*, Louis G. Fournier. *Secretary*, Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Donald J. Thorp. *Secretary-Treasurer*, Charles D. Kimball, 734 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.
- Denver Gynecological and Obstetrical Society.** (1942) *President*, Lyman W. Mason. *Secretary-Treasurer*, Jack M. Simmons, Jr., 638 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Henry A. Sincok. *Secretary-Treasurer*, Edith McCann, 425 East Wisconsin Ave., Milwaukee 2. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, P. L. Martin. *Secretary*, Albert P. Kimball, 233 "A" St., San Diego, Calif. Meetings held on the last Friday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, H. A. Wheeler, Grand Forks. *Secretary*, C. B. Darner, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Walter McMann. *Secretary-Treasurer*, L. L. Shamburger, State Health Department, Richmond, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Wayne Brehm. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Robert S. Millen. *Secretary-Treasurer*, Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Charles W. Frank. *Secretary*, Benjamin Karen, 1100 Grand Concourse, New York 56, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, C. Wendell Knudson, Medical and Dental Bldg., Seattle, Wash. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Harold V. Holter. *Secretary*, William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, A. M. McCausland. *Secretary-Treasurer*, Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, H. B. Atlee. *Secretary*, K. M. Grant. Annual meeting, June, 1950.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, George A. Palmer. *Secretary-Treasurer*, Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.
- Minnesota Obstetrical and Gynecological Society.** *President*, Russell J. Moe. *Secretary*, John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, Homer L. Pearson. *Secretary*, John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Harley E. Anderson. *Secretary*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, John W. Records. *Secretary-Treasurer*, Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Herschel Murphy. *Secretary*, Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, K. S. Tom. *Secretary*, S. Nishijima, 1221 Victoria St., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.
- Oregon Society of Obstetricians and Gynecologists.** *President*, Gerald Kinzel. *Secretary-Treasurer*, Theodore M. Bischoff, 529 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies.** (1945) *President*, Ralph E. Campbell. *Secretary*, Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.
- Dayton Obstetrical and Gynecological Society.** (1937) *President*, A. D. Cook. *Secretary*, L. O. Frederick, 413 Third National Bldg., Dayton 2, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.
- Dallas-Fort Worth Obstetric and Gynecologic Society.** (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.
- Queens Gynecological Society.** (1948) *President*, Edward C. Veprovsky. *Secretary*, George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.
- Mississippi Association of Obstetricians and Gynecologists.** (1947) *President*, R. A. Street, Jr. *Secretary*, William Weiner, Barnett-Madden Bldg., Jackson, Miss. Meetings held semiannually.
- Florida Obstetrical and Gynecological Society.** *President*, Charles J. Collins. *Secretary*, Dorothy D. Brame, Orlando, Fla. Next annual meeting, Belleair, April 10, 1949.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, J. Decherd Guess. *Secretary*, Arthur L. Rivers, 231 Calhoun St., Charleston, S. C. Meetings held in spring and fall.
- Buffalo Obstetrical and Gynecological Society.** (1946) *President*, W. Herbert Burwig. *Secretary*, Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.
- El Paso Gynecological Society.** (1948) *President*, Gerald H. Jordan. *Secretary-Treasurer*, Gray E. Carpenter, 303 N. Oregon St., El Paso, Texas.
- Kentucky Obstetrical and Gynecological Society.** (1947) *President*, W. O. Johnson. *Secretary*, Edwin P. Solomon, 910 Heyburn Bldg., Louisville, Ky.
- Indianapolis Obstetrical and Gynecological Society.** (1947) *President*, David L. Smith. *Secretary*, Sprague H. Gardiner, 314 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.
- Houston Obstetrical and Gynecological Society.** (1939) *President*, John A. Wall. *Secretary-Treasurer*, Herman L. Gardner, Hermann Professional Bldg., Houston 5, Texas. Meetings held second Tuesday of each month except July, August, and September.
- Iowa Obstetric and Gynecologic Society.** *President*, J. H. Randall. *Secretary*, William C. Keettel, Iowa City, Iowa.